Syntheses of ring A substituted ellipticines

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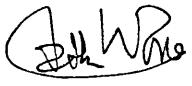
SYNTHESES OF RING A SUBSTITUTED ELLIPTICINES

submitted by KUOK KEONG VONG*

for the degree of PhD

of the University of Bath

1987



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To my parents

Acknowledgements

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Above all, I am most grateful to my parents for it is their devoted commitment and love that has been my greatest source of encouragement throughout these years and I would like to dedicate this thesis to them.

Summary

The work outlined in this thesis was conducted between October 1984 and September 1987 and is primarily concerned with the synthesis of 7- and 8-substituted ellipticine derivatives.

The starting material for the synthesis of 6-*H*-7-[3-(N,N-diethylamino)propyl]-1,4-dimethyl-9-methoxypyrido-[4,3-*b*]carbazole was 9-(N)-allyl-1,4-dimethyl-6-methoxy-carbazole which was rearranged to the 8-(C)-allyl isomer and the side chain then degraded to give 8-formyl-1,4-dimethyl-6-methoxycarbazole. The N,N-diethylaminopropyl unit was introduced *via* an Emmons Horner reaction followed by reduction while ring D of the pyridocarbazole was built up following a modified Cranwell-Saxton approach.

The nature of the rearrangement reactions of both N-allylcarbazoles and also of allyloxycarbazole have been investigated. From 6-allyloxycarbazole, 7- and 5-allyl-carbazoles are formed; these compounds could form the starting materials for ellipticines bearing solubilising side chain groups at C-8 and C-10 respectively.

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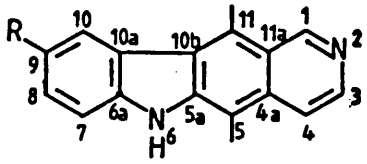
Section I

Syntheses And Biogeneses

Of Ellipticine And Its Derivatives

1.1 Background

The alkaloid ellipticine 1 (6H-5,11-dimethylpyrido-[4,3-b]carbazole) was first isolated in 1959 from the leaves of Ochrosia elliptica Labill. (family Apocynaceae), a plant harvested at a United States Department of Agriculture Plant Introduction Station in Florida (1) (It grows wild in Oceania.)



1 R=H
2 R=OMe

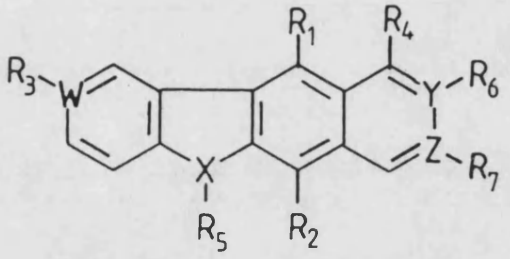
Later, in an examination of Australian plants for substances with antitumour activity, scientists at the Cancer Chemotherapy National Service Centre of National Institutes of Health, in the U.S.A. obtained extracts from two botanically related species, Ochrosia moorei F. Muell. and Excavatia coccinea (Tejs. & Bin.) Mgf. (family Apocynaceae). From these extracts, several alkaloids, in particular, ellipticine 1 and 9-methoxyellipticine 2 were isolated. These alkaloids were shown to account for the activity of the extracts against the experimental tumours Sarcoma 180, Adenocarcinoma 755, and Lymphoid leukaemia L1210 in mice and they also exhibited activity against human

carcinoma of the nasopharynx carried in cell culture (2).

Since then the isolation of ellipticine and related compounds from various other species of the genera Aspidosperma, Tabernaemontana and Strychnos of the Apocynaceae have also been reported (3-11).

In 1959, Woodward et al. published the first total synthesis of ellipticine thus confirming its tetracyclic structure (12). Now almost three decades have elapsed, yet work on this family of compounds continues apace and many new facets of the biology of the ellipticines are being unravelled, ~~much results accumulated~~. Much of the early synthetic work has been summarised in reviews and other publications (13-16) and as might be expected for compounds with interesting pharmacology, many workers have sought, and seek, to provide short versatile preparative routes to them. The biogenesis of the ellipticines is also of interest (17) not least because there is an unusual number of and disposition of carbon atoms between C-3 of the indole unit and the pyridine nitrogen. The normal precursor of indole alkaloids is tryptophan with two carbon atoms in the side chain.

As well as many derivatives of ellipticine itself, some analogues, e.g. 3-7, have also been synthesized (18-20) (Figure 1). These will not be discussed here where the focus of attention will be pyrido[4,3-b]carbazole chemistry and biochemistry.



1	$R_1=R_2=Me$	$R_3=R_4=R_5=R_7=H$
	$Y-R_6=X=N$	$W=Z=C$
3	as 1, except:	$R_4=Me$, $R_1=H$
4	as 1, except:	$X-R_5=O$
5	as 1, except:	$X-R_5=S$
6	as 1, except:	$W-R_3=N$
7	as 1, except:	$R_6=H$, $Y=C$, $Z-R_7=N$

Figure 1

1.2 Biogeneses of ellipticine

The study of the biological origin of an alkaloid is both fascinating and challenging in its own right. In an age when biotechnology is growing fast, ideas of employing living matter as production lines to generate useful chemical products are being constantly put forward. This also demands a sufficient knowledge of the biosynthesis of these products. A common difficulty associated with the determination of biogenetic pathways in higher plants is the lack of supporting experimental evidence. There is no exception in the case of ellipticine (17,21).

Ellipticine 1 and its natural isomer olivacine 3 usually co-occur with uleine 10 (22) and apparicine 9 (23). It is therefore presumed that these alkaloids have the same progenitor (16) and Wenkert in 1962 and Potier et al. in 1973 have each put forward proposals to account for their biogenesis (24,25).

Potier's hypothesis, based upon a biological version of the Polonovski reaction is the most recent (26-29); he envisages that stemmadenine-N-oxide 8 is the key intermediate. This is presumed to undergo a modified Polonovski type reaction to give a number of indolenium products which variously cyclise to the four congeners ellipticine 1, olivacine 3, apparicine 9 and uleine 10 (Figure 2).

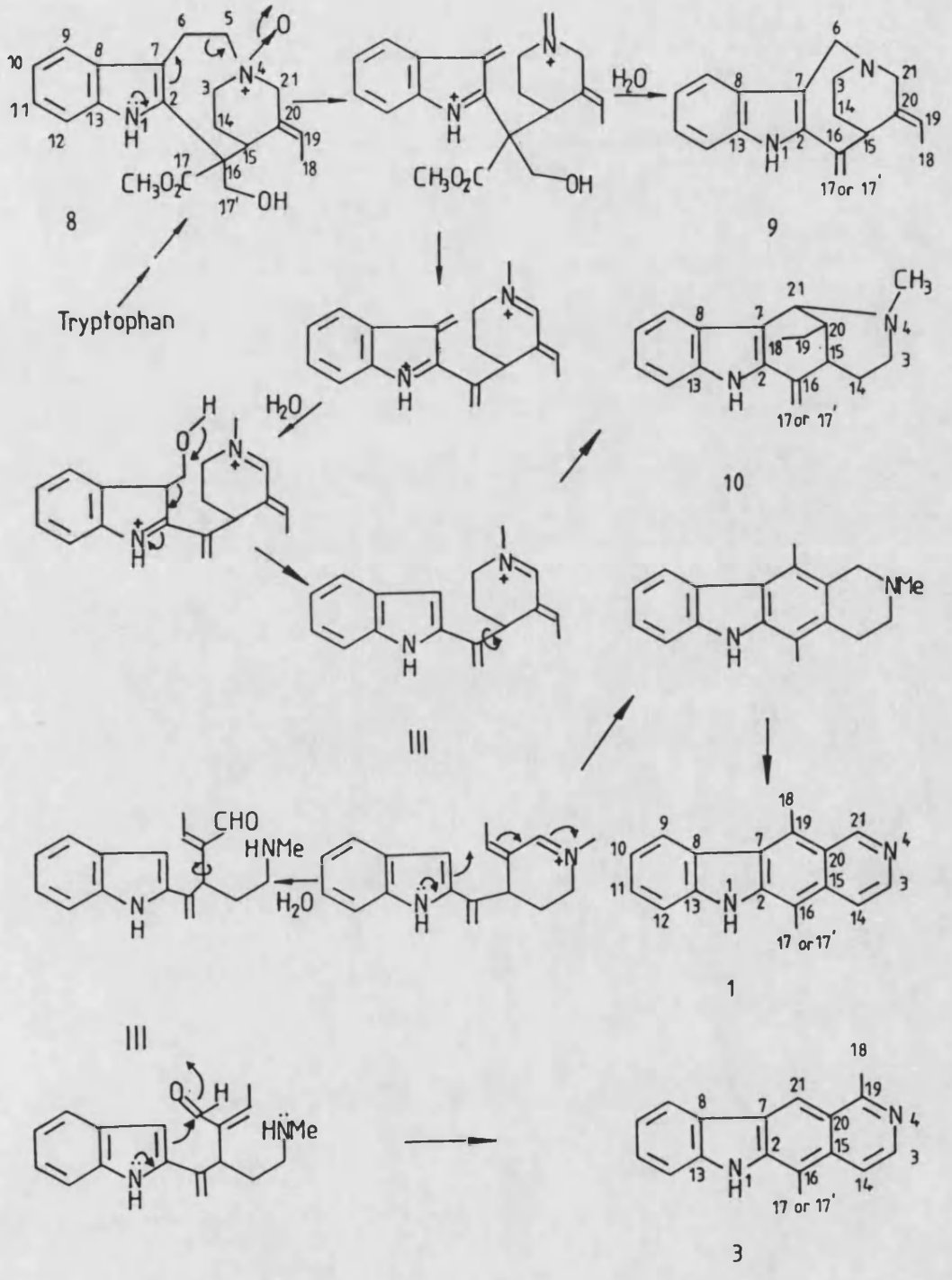


Figure 2

In an alternative proposal, Wenkert (24) also postulates a common precursor, **15**, but this is derived from an anthranilic acid derivative **13** and a seco-prephenateformaldehyde (SPF) unit **11** or more likely, secologanine **12**. Cyclisation of this precursor first to an indole **14** and then to an iminium species **15** might ultimately afford the same series of alkaloids (Figure 3) although it should be noted that appariciné **9** is not included.

As stated earlier, tryptophan is considered to be the usual source of the indole ring of most alkaloids and naturally there has been some controversy over which, if either, scheme is correct. Sadly despite some effort, the biosynthesis of ellipticine remains in doubt, although there are claims that a very weak incorporation of tryptophan into stemmadenine and uleine has been observed. The incorporation of labelled substrates into higher plants is notoriously difficult so this result is not surprising, and no new work in this area has been presented to resolve the problem.

1.3 Syntheses of ellipticine and its derivatives

Since 1959, much has been committed to the exploration of general and efficient synthetic routes to ellipticine and its derivatives. As a result, a large number of routes have been developed. These have been reviewed by Sainsbury (13), Shannon *et al.* (14), Gribble (15) and Potier *et al.* (16).

Hence, only a selection of the routes will be presented here. Indeed it is debatable whether effort should still be directed towards the synthesis of ellipticine itself since a number of convenient routes are now available.

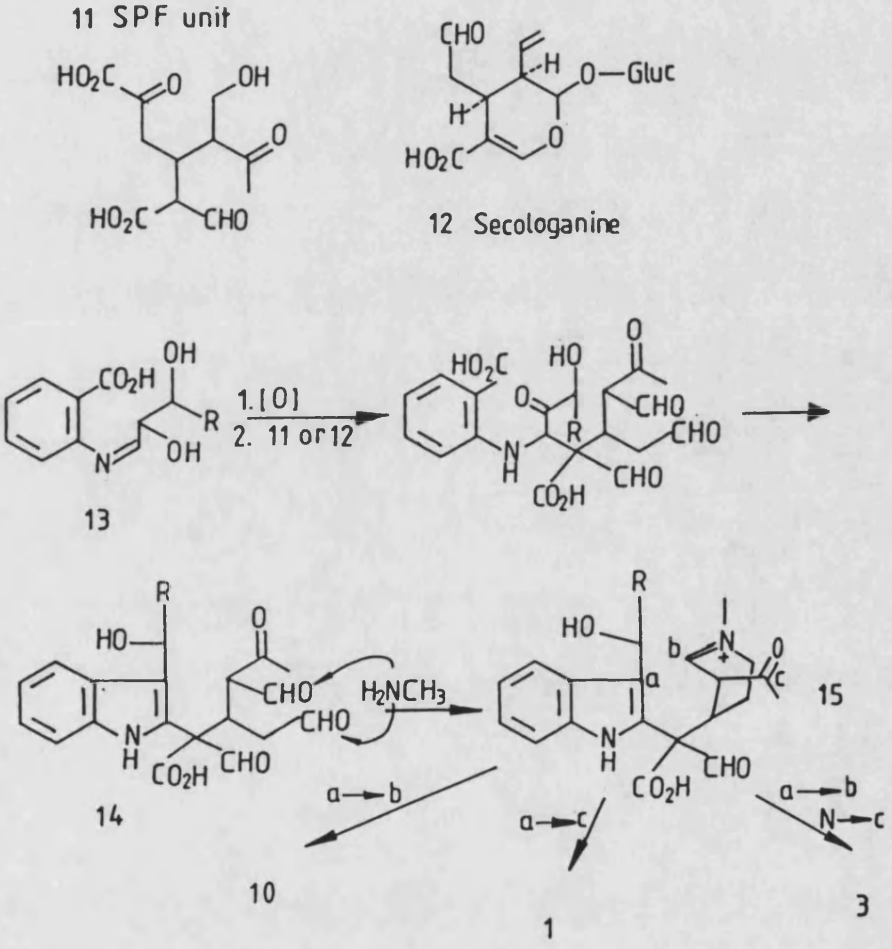
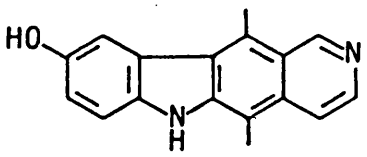
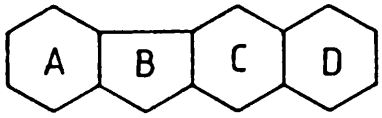


Figure 3

It has been shown that 9-hydroxyellipticine **16**, a major metabolite of ellipticine in the rat (30), is forty times more active than ellipticine against leukaemia L1210 implanted in mice (31-32) and recently, other more active ellipticine derivatives have also been reported (33). As a result, current synthetic interests have shifted towards the construction of derivatives that contain substituents more likely to impart even greater activity or to improve solubility in aqueous media, and hence ease of administration to the patient.



16



The most popular method of classification of the various synthetic strategies was introduced by Sainsbury (13) who divided the approaches into three types: B, C and D based upon the last ring to be constructed in the synthesis. A fourth type, i.e. B+C was later added by Potier *et al.* to include a new synthetic method in which two rings, B and C, are simultaneously formed as the last step (16).

1.3.1 B Type syntheses

Only a few routes fall into this catagory yet this is one of the first avenues to be explored. For example, Woodward and Stillwell (34) designed a synthesis of ellipticine that required a Fischer indole ring forming reaction as the key step (Figure 4). Unproductive in their hands, it was later successfully exploited by other workers (13-14).

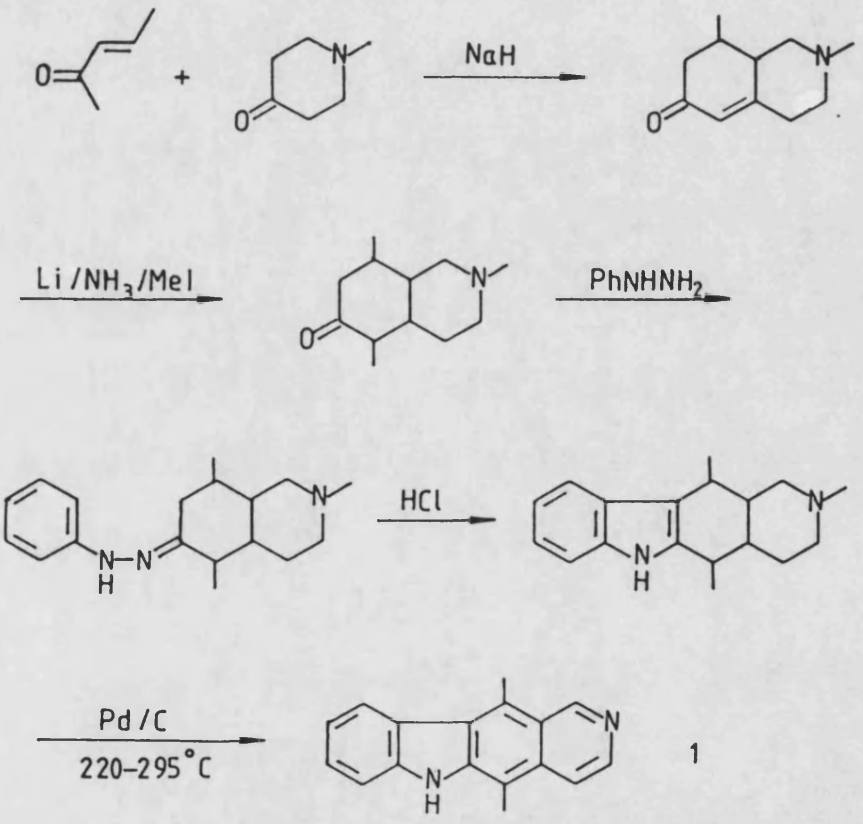
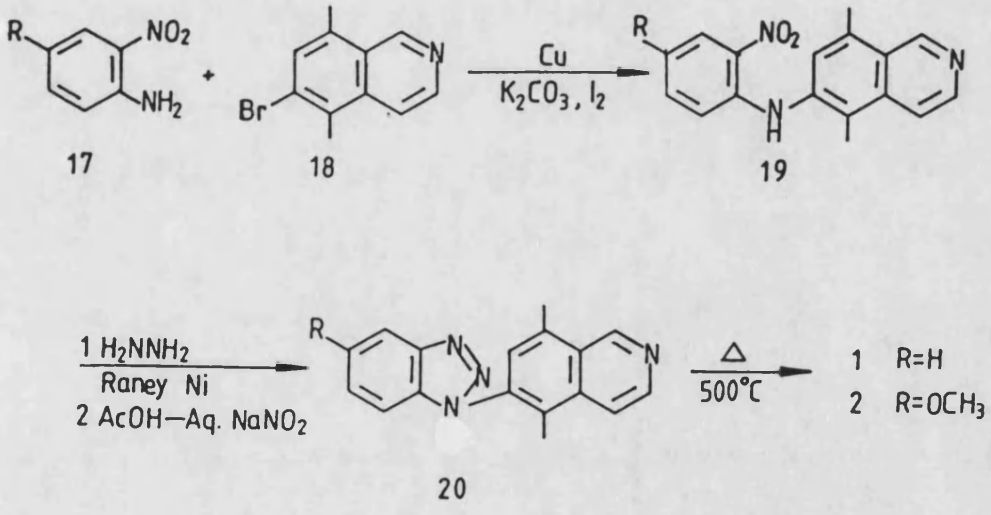


Figure 4

Another related strategy was considered by Bisagni et al. (19,35-37) which they regularly employed for the syntheses of 9-aza-analogues of ellipticine, 6. Perhaps the best of these approaches is that of Miller and co-workers (38) who have described syntheses of both ellipticine 1 and 9-methoxyellipticine 2 (Figure 5). In this work, substituted nitroanilines 17 are coupled with 6-bromo-5,8-dimethylisoquinoline 18 under Goldberg's condition to furnish the corresponding diarylamines 19. Reduction of the nitro group in these products with hydrazine hydrate/ Raney-Ni, followed by diazotisation gives the benzotriazoles 20 which are pyrolysed at 500°C to yield the required tetracycles (39). The key starting intermediate 18 is not readily available, and many steps are involved in its production.



17 18 19 20

Figure 5

Workers in this laboratory have shown that Miller's work is very reliable, but the labour required in the preparation of this isoquinoline **18** severely limits the attraction of this synthesis, to say nothing of the need for a very high temperature in the pyrolysis step. The latter factor tending to rule out this route for the synthesis of more complex and labile analogues.

Previously, Miller *et al.* had reported another approach which, unfortunately gave the undesired structural isomer as the major product (40). In this route, the azido compound **21** was chosen as the nitrene precursor and upon heating to 180-200 °C, it gave two isomers: ellipticine **1** and the indolenine **22** in a ratio of 1:3 (Figure 6).

This result contrasts with the observation that when the biphenyl azide **23** is thermolyzed, 1,4-dimethyl-carbazole **24** is the only product isolated. Indeed no 3,3-di-substituted indolenine was detected in the ^{1}H n.m.r. spectrum of the crude reaction mixture. It is obvious that the pyridine nitrogen atom has a major influence on the electron availability within Miller's assumed intermediate.

1.3.2 C Type syntheses

This is the largest class of all (13-16), not surprisingly since the starting materials are preformed indoles and pyridines. Woodward was the first to see the attractiveness of using indole **25** and 3-acetylpyridine

26 as starting materials (12) in his synthesis (Figure 7). However, the last two of the three steps involved did not prove satisfactory and the overall yield in the Harvard synthesis was less than 2%. The synthesis has never been used subsequently, but its simplicity has served as an inspiration for other workers, particularly those at Bath.

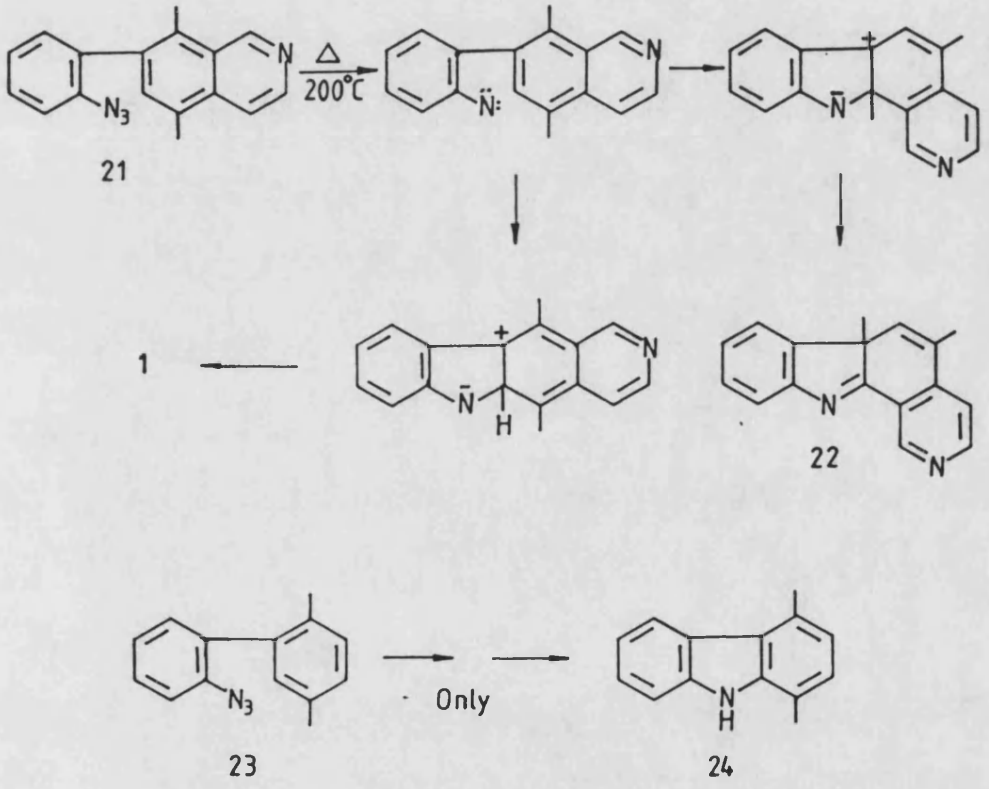


Figure 6

An interesting development has emerged from the laboratory of Snieckus (41) who has reported a route which employs a so-called "tandem-directed metalation" sequence. Several N-protected 3-formylindoles **27** were allowed to react with lithiated N,N-diethylisonicotinamide **28** to yield the corresponding indolopyridobenzoquinones **29-31**. The yields are found to be inversely proportional to the ease of removal of the protective group R. The quinones were then transformed individually in a three-step sequence, without purification of intermediates, into the appropriate pyridocarbazoles **32**, **33** and **1** (Figure 8). The quinones **29-31** are handy precursors of simple ellipticines. Other workers have also recognised this fact and devised alternative routes to them (42,43).

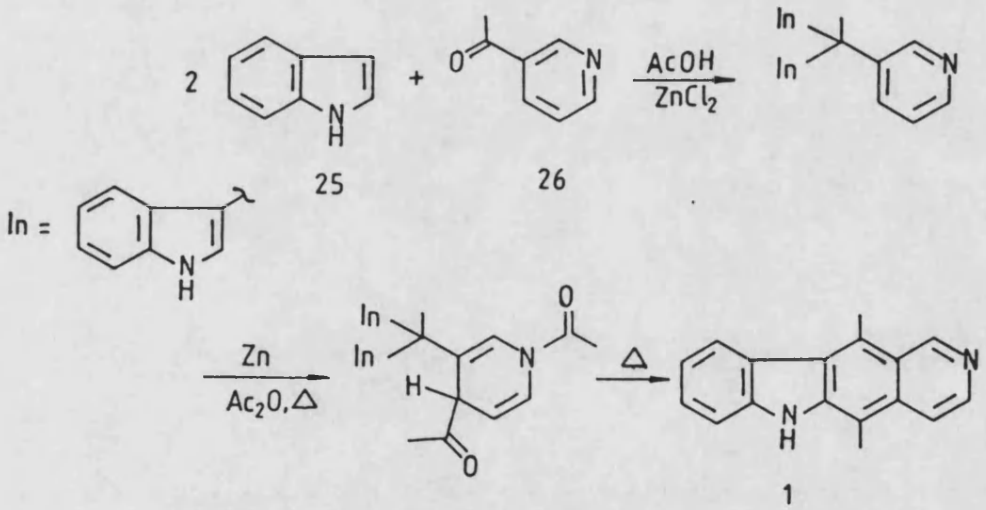
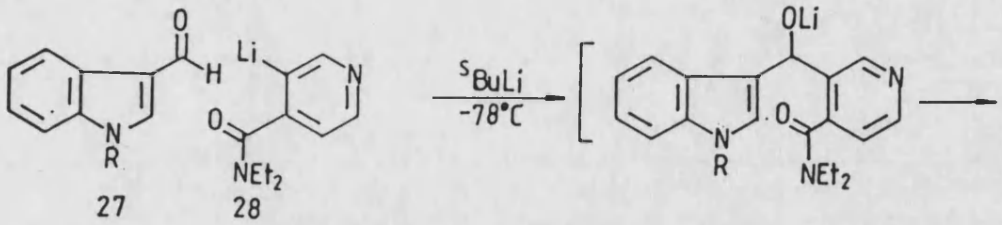
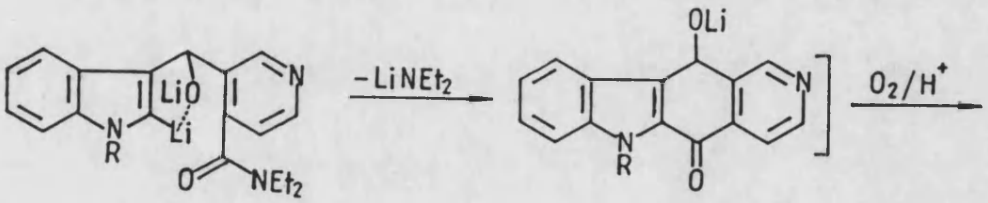
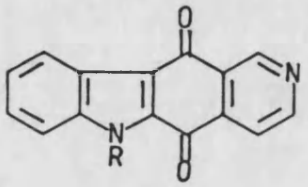


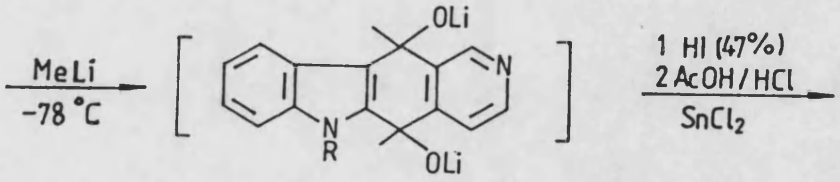
Figure 7

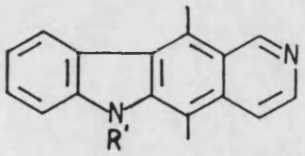






	R	%Yield from
29	Me	76
30	CH_2Ph	44
31	CH_2OMe	26





	R'	% Yield from
32	Me	62
33	CH_2Ph	40
1	H	40

Figure 8

Gribble *et al.* have also reported a related methodology for the syntheses of some 5-substituted ellipticines (44,45). Thus, by the reaction of 2-lithio-1-phenylsulphonylindole **35** with cinchomeronic anhydride **36** at -100°C, these workers have obtained the ketolactam **38** which then yielded a diastereomeric mixture of diols **39** (R_1=R_2=Me) on treatment with excess methyllithium. These diols were converted to ellipticine **1** by the action of sodium borohydride, thereby affording a 54% overall yield of the tetracycle (Figure 9).

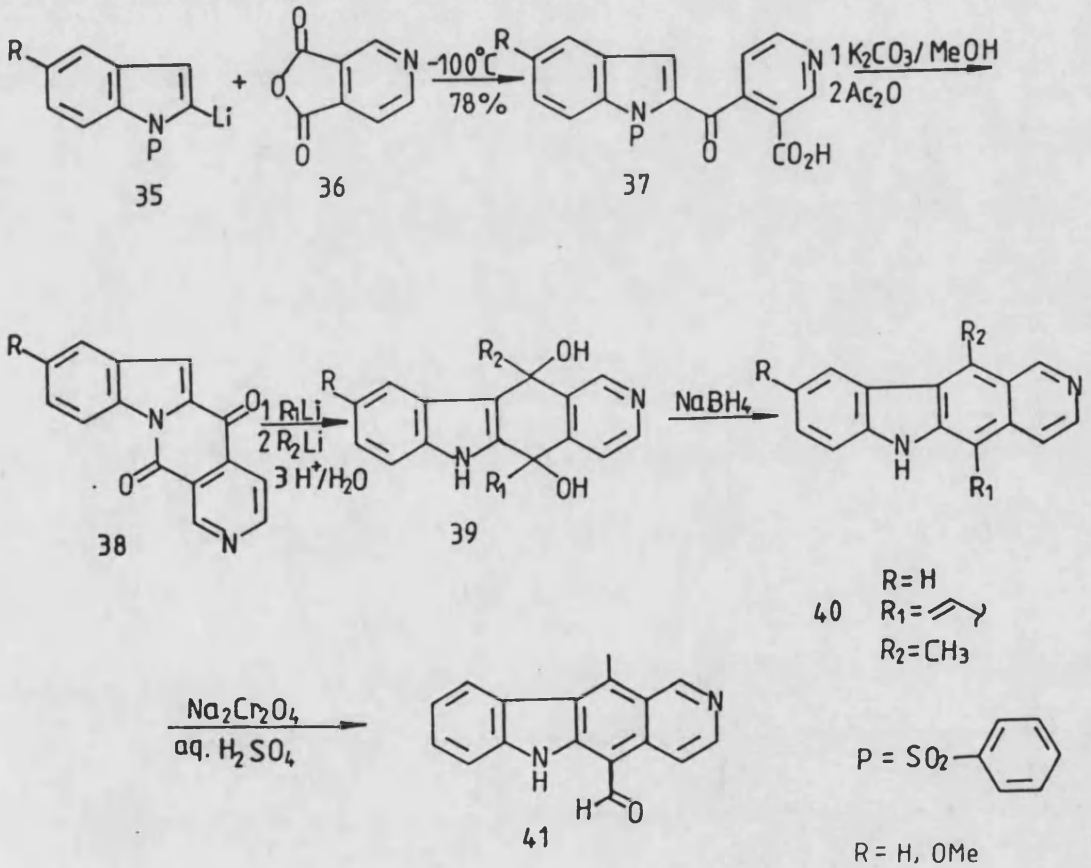


Figure 9

Repetition of the sequence with 5-methoxyindole gave 9-methoxyellipticine **2** in 47% overall yield.

In addition, it was also shown that the synthesis allows the manipulation of the substitution pattern at C-5 and C-11 because the carbonyl groups of the quinones **38** exhibit different reactivities toward alkyl lithiums. This is due to the fact that one of them is less amidic then the other. Exploiting this observation, Gribble and his colleagues (45) have reported a total synthesis of 5-oxoellipticine **41** through oxidative cleavage of 5-vinylellipticine **40**. The formyl compound **41** has also been recently synthesized by Archer *et al.* by another approach (46).

Many workers have considered the construction of ring C *via* a Diels-Alder cycloaddition reaction, but all the published results indicate a lack of regioselectivity. Nonetheless, in Moody's synthesis (47), the low yield of ellipticine obtained is compensated by the brevity of the route (Figure 10). Thus 3-(3,3-dimethyltriazen-1-yl)-pyridine-4-carboxylic acid **44**, a precursor of 3,4-pyridyne **43**, was reacted with the diene, 1,4-dimethylpyrano-[3,4-*b*]indol-3-one **42** to give a 50:50 mixture of ellipticine and isoellipticine **7** in 40% yield.

Similarly, in a related synthesis, Gribble *et al.* (50) reacted pyridyne **43** with 1,3-dimethyl-4-(phenylsulphonyl)-4H-furo[3,4-*b*]indole **45** to give ellipticine **1** and isoellipticine **7** in approximately equal yields (Figure 11).

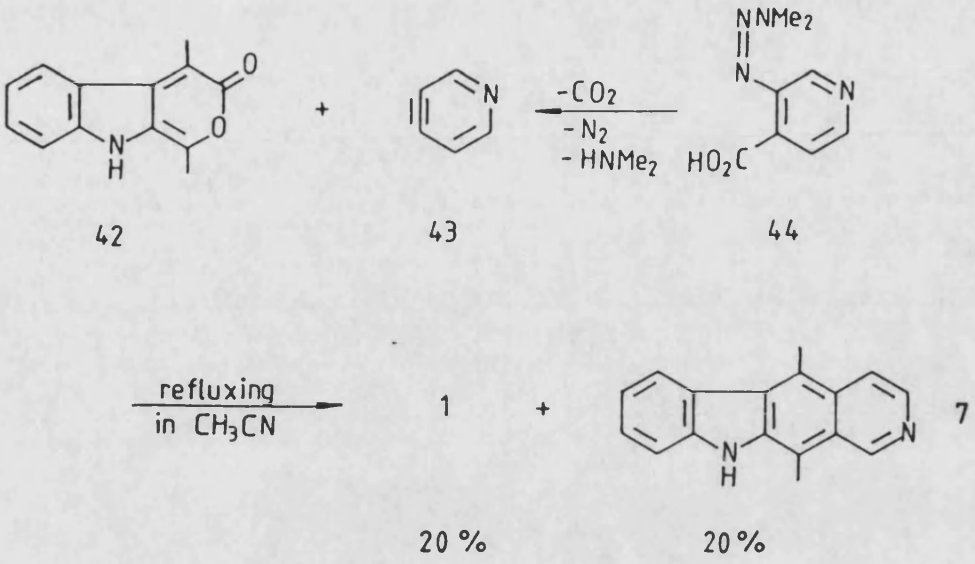


Figure 10

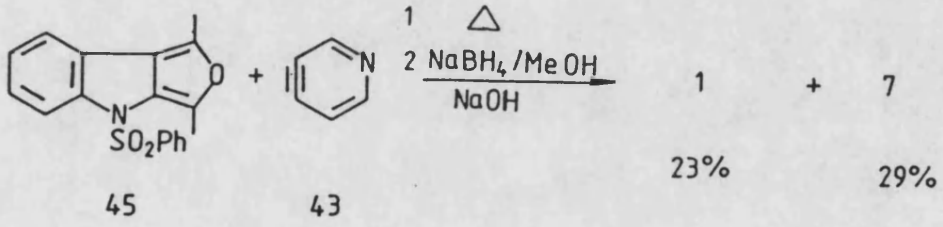


Figure 11

In recent years, attention has been focussed on the introduction of more elaborate groups into the C ring in order to improve the theraputic index of the ellipticines. An illustration is provided by the work of Pandit (49). Here the exocyclic methylene compound **47** was prepared in seven steps from N-methylindole **46** and subjected to

N-chlorosuccinimide, aqueous potassium hydroxide and thionyl chloride. This eventually resulted in the formation of the chloromethylellipticine **48**. Displacement of the chlorine atom by various nucleophiles, such as substituted amines and carbohydrates, furnished derivatives of 6-methylellipticine that bear various substituents at the C-11 position, **49-52** (Figure 12). The same workers later commented that direct lithiation at the C-11 methyl group of 6-methylellipticine **32** was possible using lithium diisopropylamide at -78°C (50). Hydroxymethylation of the lithiated intermediate with formaldehyde then gives the hydroxy derivative **53**. Glycosides **54-56** were subsequently prepared by coupling the product with the appropriately derivatized sugar using tin tetrachloride as catalyst (Figure 13). None of these compounds are ring A hydroxylated and Pandit *et al*. recognising the importance of hydroxy group at the C-9 position for anticancer effect, sought to develop an indirect 9-hydroxylation procedure (51). In a demonstration of this technique, 6-methylellipticine **32** was formylated at the C-9 position and this product subjected to the conditions of the Baeyer-Villiger rearrangement with hydrogen peroxide and sulphuric acid in methanol. This gave 9-hydroxy-6-methylellipticine **58** in greater than 90% yield! Under these conditions, the pyridine nitrogen was not oxidized (Figure 14).

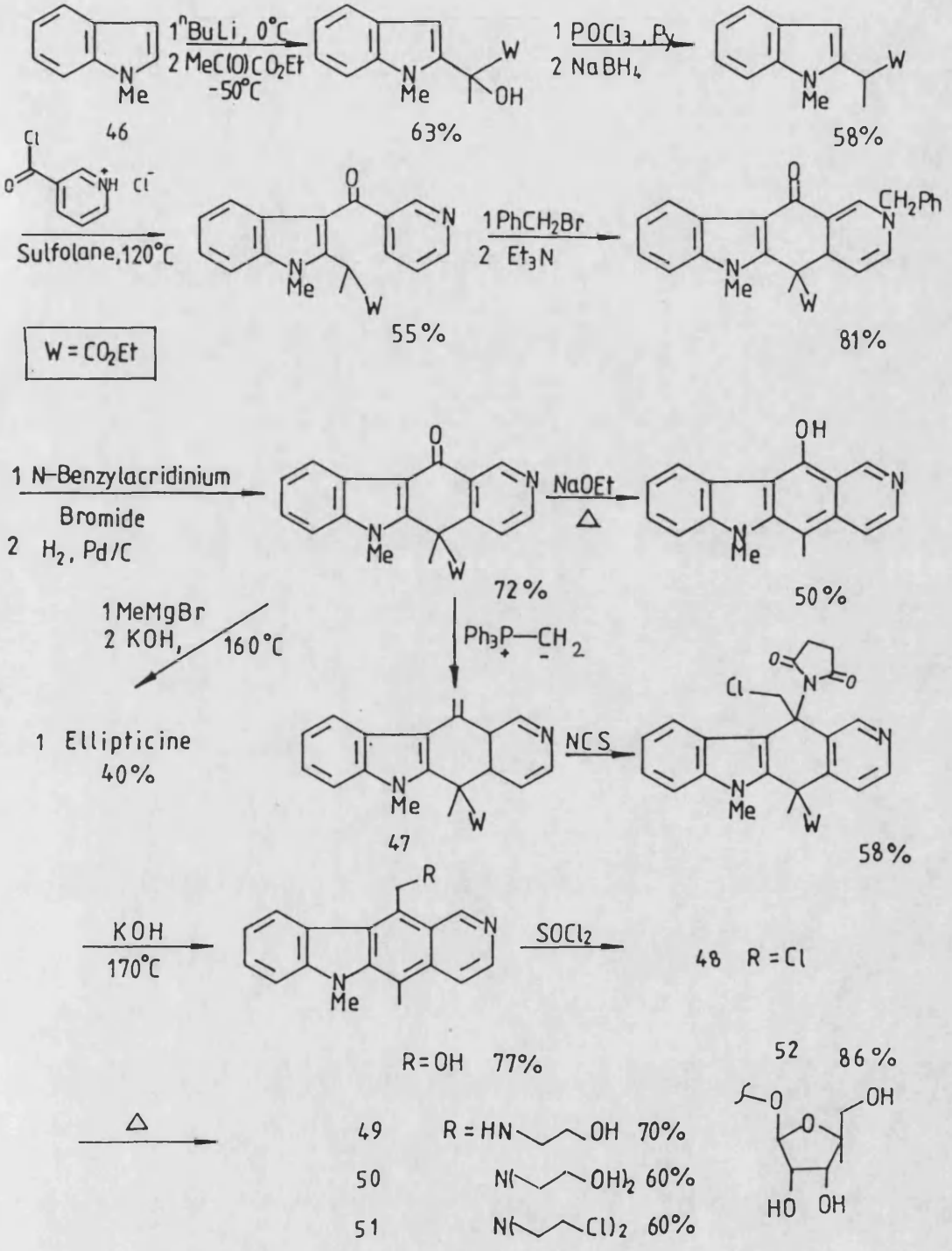

1 nBuLi, 0°C
2 MeC(O)CO2Et
-50°C
63%
1 POCl3, Py
2 NaBH4
58%
46
Sulfolane, 120°C
55%
1 PhCH2Br
2 Et3N
81%
W = CO2Et
1 N-Benzylacridinium Bromide
2 H2, Pd/C
72%
NaOEt
50%
1 MeMgBr
2 KOH, 160°C
1 Ellipticine
40%
Ph3P—CH2
NCS
58%
47
KOH
170°C
SOCl2
48 R = Cl
R = OH 77%
52 86%
49 R = HN OH 70%
50 N(OH)2 60%
51 N(Cl)2 60%

Figure 12

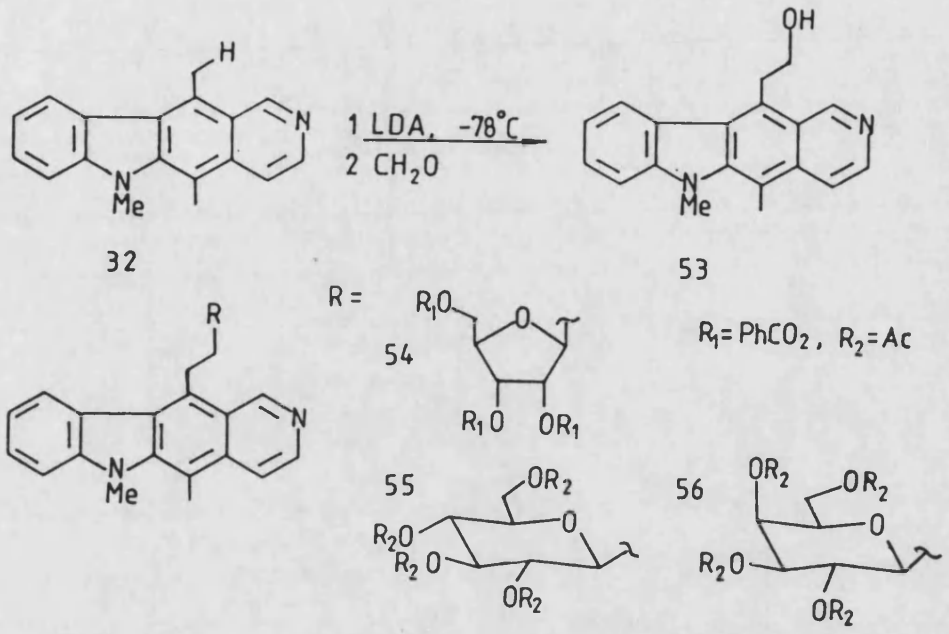


Figure 13

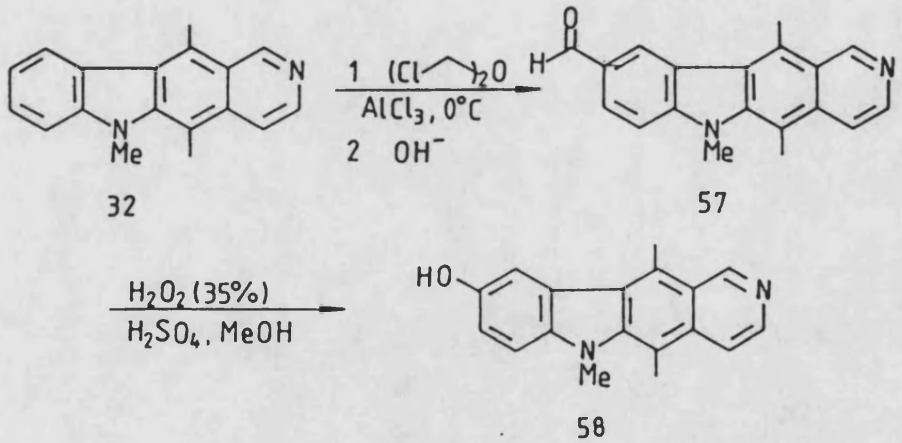


Figure 14

However, it has to be noted that the utility of all the methodologies developed by Pandit depend greatly on the success of replacing the 6-methyl group with other easily removable protecting groups. 6-Substituted ellipticines are not effective anticancer agents and Pandit, significantly, did not claim useful activity for his products. In view of this well established fact, it is hard to see why the Dutch workers did not protect the indolic nitrogen atom with a more easily removable group. It would have also been sensible to have had the 9-hydroxyl group, or its equivalent, in place early in the synthesis.

At a glance, it seems many of the C type routes can easily be extended to the syntheses of ellipticine derivatives with various substitutions on the A ring, simply by replacing indole with other appropriately substituted indoles. However the range of substituted indoles supplied commercially is very limited, and some of them can be very expensive.

Indeed, syntheses of some substituted indoles are not always straightforward (52). The following methodology developed by Sainsbury *et al.* seems to have solved this problem, and it has been used in recent years to synthesize a number of ellipticine derivatives **65-67** with various substituents on the A ring (53). More recently, an application of the same route, has afforded compounds **68-69** with unusual groups at C-5 (54,55). The entire route can be divided into two major stages: to the synthesis

of pyridylaldehyde 60, which is then reacted with an arylhydrazine 59 in the presence of methanolic hydrogen chloride. Hydrazone formation is immediately followed by Fischer indolisation to give the pyridylethylindole 61 in ca. 60-80% yield. These products are substituted at the pyridine nitrogen atom with an easily cleavable group which also facilitates the nucleophilic addition of cyanide ion at the 4-position of the resulting pyridinium salt 62. Exposure to sunlight is usually sufficient to generate the nitrile 63, which react with alkyl lithiums to yield imines 64. These are easily hydrolyzed to the corresponding ketones by heating with acetic acid, but the carbonyl compounds are never isolated, undergoing spontaneous ring closure to the ellipticine targets (Figure 15).

Regio-control over the indolisation of hydrazines having two available ortho sites is normally impossible. Thus the meta-substituted methoxyphenylhydrazone 70 yields a mixture of the methoxyellipticines, 71-72, the former predominating (Figure 16). Unfortunately, mixed ellipticines are not easily separated one from the other.

1.3.3 D Type syntheses

Synthetic routes of this type are few and have mainly been used to synthesize olivacine 3 and its derivatives (56,57). Two major exceptions are discussed below.

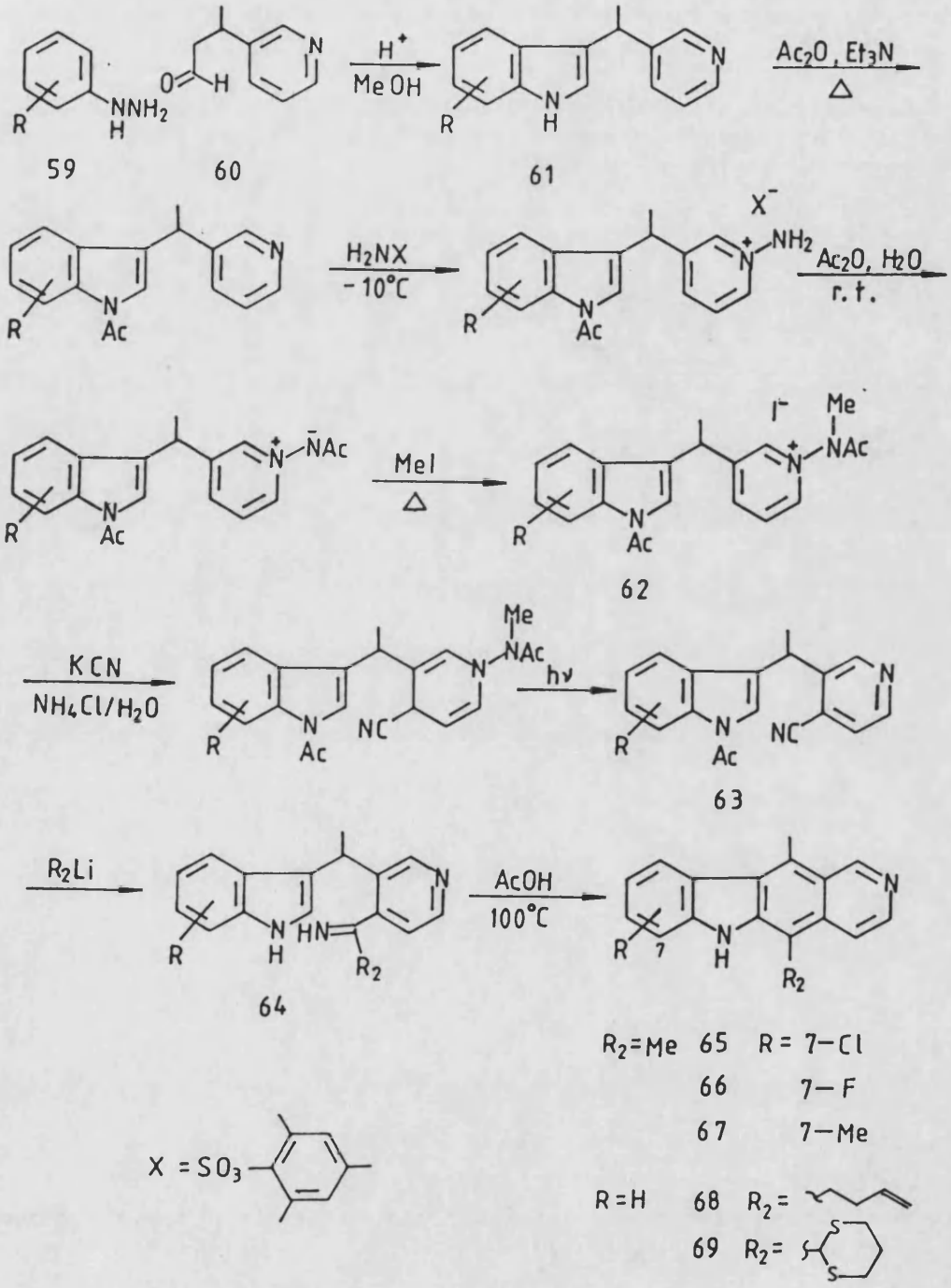

H+
MeOH
Ac2O, Et3N
△
59
60
61
H2NX
-10°C
Ac2O, H2O
r.t.
MeI
△
62
KCN
NH4Cl/H2O
hν
63
R2Li
AcOH
100°C
64
R2=Me 65 R = 7-Cl
66 7-F
67 7-Me
R=H 68 R2=
69 R2=
X = SO3

Figure 15

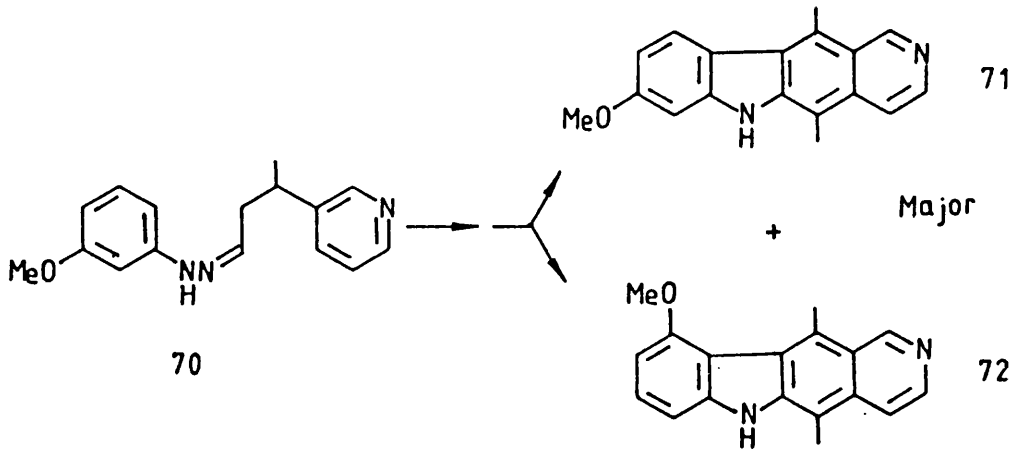


Figure 16

Cranwell and Saxton have reported a very efficient synthesis of 1,4-dimethylcarbazole 24 (R=H) from indole and 2,5-hexadione 74 and converted it into ellipticine 1 (58). Over the years, their work has been adopted and improved on so that a number of simple ellipticine derivatives have been produced in bulk and used for pharmacological evaluation (2). There is no doubt that the Cranwell and Saxton route is the most popular ellipticine synthesis of all, yet is one of the oldest. Two problems attend it, however; originally the carbazole was C-formylated and converted into the corresponding imines 77. Direct cyclisation of these products was very inefficient so it was necessary to reduce them to the related amines 78, ring close and reoxidise the dihydroellipticines so formed. This sequence added undesirable length to the route. Secondly where the carbazole contains electron donating groups, these may

affect the site of formylation. In order to address the first problem, Shannon et al. (59) have taken the amines 78 and reacted them with 4-toluenesulphonyl chloride. When the N-tosyl derivatives 79 are heated with acid, ring closure is followed by elimination of 4-toluenesulphinic acid to give the ellipticines 81 directly (Figure 17).

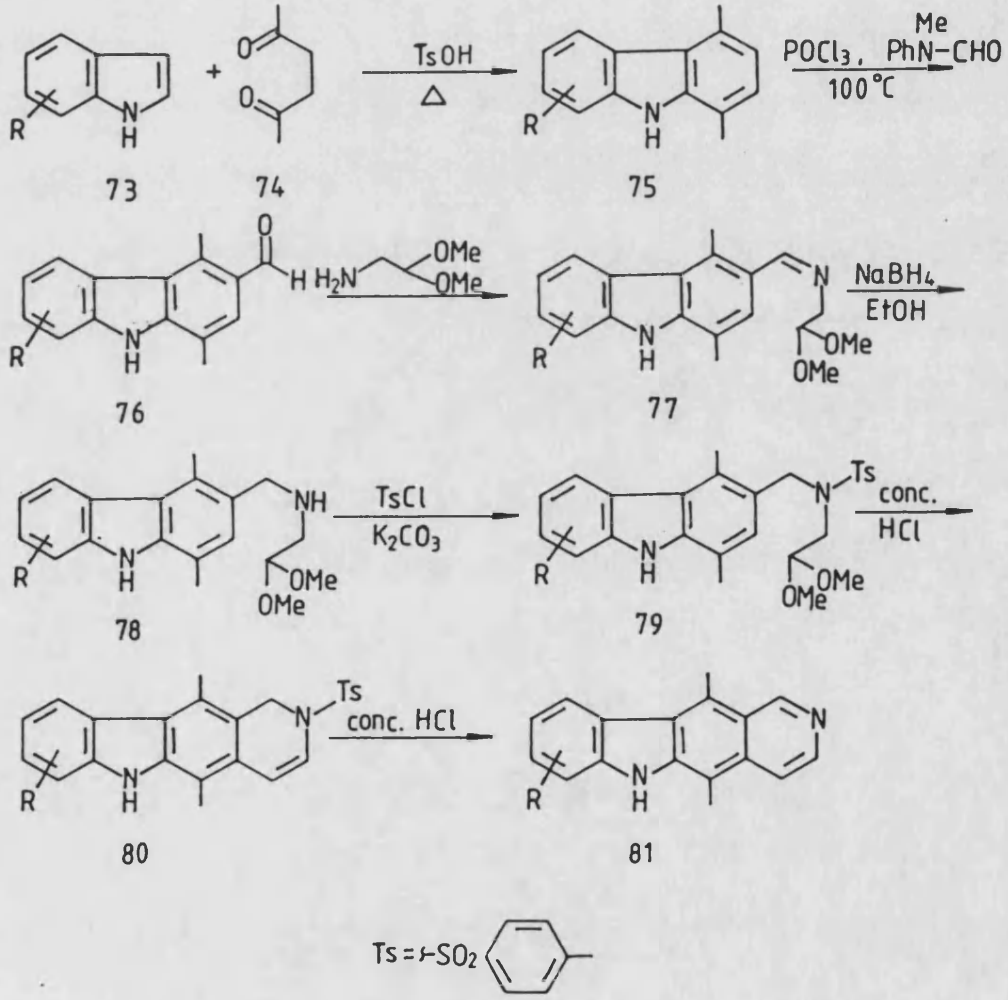
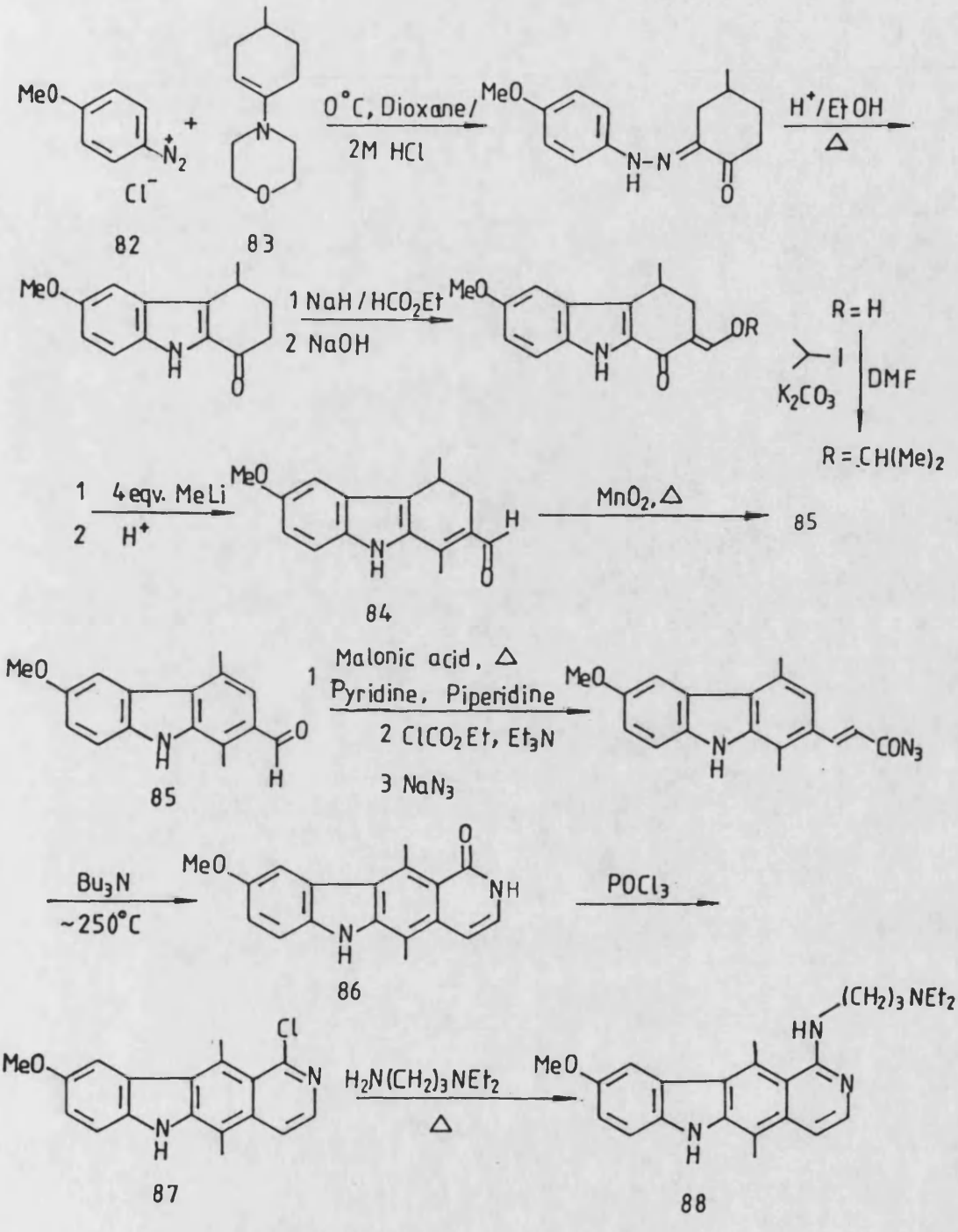


Figure 17

In this way the handling problems associated with 1,2-dihydroisoquinoline derivatives are avoided, this is important since these compounds tend to disproportionate and also to react with oxygen giving isocarbostyrils.

The second problem have been tackled by Bisagni et al. (60) and is employed to prepare 1-amino substituted ellipticines (Figure 18). For example, the dihydrocarbazole **84** was prepared in five steps (11% overall yield) from 4-methoxybenzenediazonium chloride and 4-methyl-1-morpholinocyclohexene and oxidised to the carbazole **85** using manganese dioxide. The exact location of the formyl group is now pre-arranged so that the remaining annulation reactions can only afford an ellipticine. This is, however, hardly a practical approach since the construction of the dihydrocarbazole is by no means a trivial procedure. But in this case, Bisagni wished to functionalise the C-1 site of the targeted tetracycle and the isocarbostyril **86** seemed to be a desired intermediate. Unfortunately, treatment of this compound with phosphorus oxychloride gave the 1-chloroellipticine **87** in only 25% yield. Whereas a 73% yield was obtained in the same reaction in the olivacine series where a methyl group is not present at the C-11 site, thus presenting no steric problem for the reaction. The side chain was subsequently introduced by condensing the chloroellipticine with 3-N',N'-diethylaminopropylamine to afford the product **88**.



2.3% overall yield

Figure 18

1.3.4 B+C Type syntheses

Ghosez et al. (61) have reported the only example of this type of ellipticine synthesis (Figure 19). The acid chloride **89** and the aniline **90** in the presence of triethylamine yielded 75% of crude anilide **91**. To avoid any loss of material, the crude anilide was used directly to generate the vinylketenimine **92** which when heated, underwent intramolecular cycloaddition to yield the tetrahydropyridocarbazole **93** which was reduced to the tetrahydroellipticine **94**. The latter compound has previously been converted to ellipticine in low yield, by other workers (62). Although this route is highly convergent, its applicability has yet to be proven.

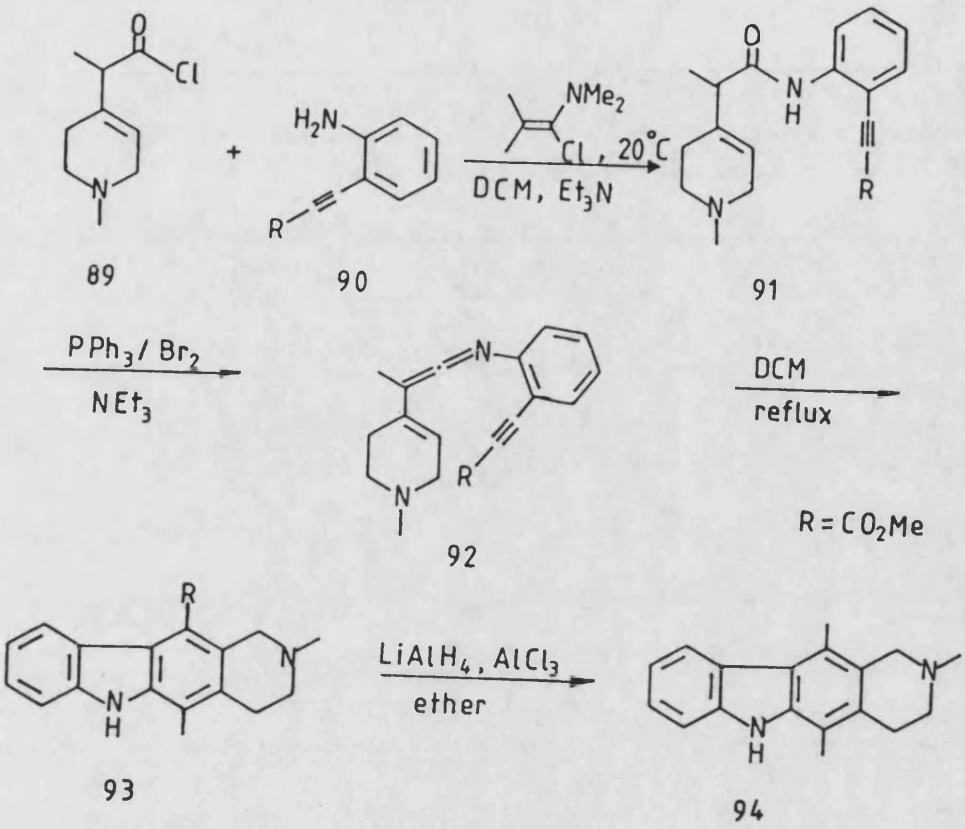

O
Cl
N
+
H_2N
R
NMe_2
Cl , 20°C
DCM, Et_3N
O
N
H
R
N
89
90
91
PPh_3 / Br_2
NEt_3
N
R
N
92
DCM
reflux
R = CO_2Me
R
N
H
93
$LiAlH_4$, $AlCl_3$
ether
N
H
94

Figure 19

Section II

Biological And Pharmacological Properties Of Ellipticine And Its Derivatives

2.1 Antitumour activity of ellipticine and its derivatives

The majority of the thirty or so currently clinically useful anti-neoplastic drugs are believed to interfere with aspects of DNA function (63-66). Those compounds that directly interact with DNA constitute an increasingly important group of such drugs, and are exemplified by cis-platinum, amsacrine, bleomycin and doxorubicin, as well as the more traditional alkylating agents. Interference with the processes of DNA transcription, replication, RNA synthesis and topoisomerase action, have been variously noted for these agents; the precise mechanisms whereby they have a selectivity for tumour cells remain unclear, although their differential effect on rapidly-proliferating cells is an important factor.

Ellipticine is a natural antitumour antibiotic which is being tried and further developed for human anticancer treatment. There is a great need for new DNA-reactive anticancer drugs because of the narrow spectrum of activity and narrow theraputic index of current drugs, many of which fall into the six rather artificial categories:

a. alkylating agents and analogues
b. nitrosoureas and analogues
c. antimetabolites
d. cytotoxic antibiotics

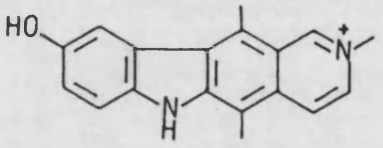
e. Vinca alkaloids and analogues

f. biological reponse modifiers

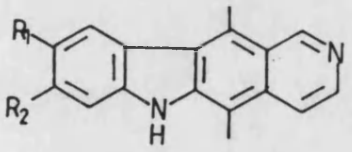
Reduction of toxic side effects and an improvement of target specificity are the two important goals in drug research. Relating to the former aspect, trials with ellipticines in animals have shown minimal toxicity with useful antitumour activity. Trials in man have confirmed that the ellipticines are not myelotoxic, but unfortunately, they do have other dose-limiting toxic effects (67).

Considerable interests in the medicinal value of 6H-pyrido[4,3-b]carbazoles began after the disclosure of the useful inhibitory properties of ellipticine and 9-methoxyellipticine against a variety of cancerous tumours (68). Thus, ellipticine and its derivatives have been shown to inhibit the growth of various experimental tumours, for example the Walker 180 sarcoma, Adenocarcinoma-755, L-1210 leukaemia and myeloblastic leukaemia (2,69-71). Since then, it has been established that some skeletal modifications of ellipticine diminish its antitumour effect (2,72-75). For instance, the presence of methyl groups at the C-5 and C-11 positions are necessary for the manifestation of cytotoxic effect on mice leukaemic L1210 cells (33,75). The quaternisation of the pyridinium nitrogen of 9-hydroxyellipticine has furnished a highly active compound, 9-hydroxy-N-2-methylellipticinium acetate **95** (76) which has recently been used, for example in the treatment of

osteolytic metastases of human breast cancers (77-78). 9-Hydroxyellipticine is forty times more active than ellipticine against murine L-1210 leukaemia whilst the corresponding 7-substituted isomer is six times less active than ellipticine (79). It is interesting to note that 8,9-methylenedioxy- **96** and 8,9-dimethoxyellipticine **97** (Figure 20) exhibit no antitumour activity against the solid form of Walker sarcoma 180 and that of Ehrlich carcinoma in mice. In addition, various esters **98** of 9-hydroxy-ellipticine show either weak or no activity (68).

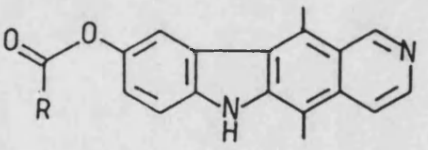


95

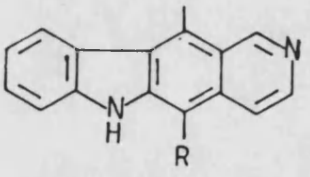


96 $R_1R_2 = OCH_2O$

97 $R_1 = R_2 = OCH_3$



98 R = Me, Et, Ph, etc.



99	R =	CH_2OH
100		$CH_2OC(O)NHMe_2$
101		CO_2Me

Figure 20

A comparative study of the mutagenic and cytotoxic activities of various ellipticine derivatives has been made by Paoletti et al. (79) using the Chinese hamster ovary cell hypoxanthine-guanine phosphoribosyltransferase assay (CHO/HGPRT assay) and on tests with Salmonella. They have shown that ellipticine, 9-methoxyellipticine, 9-hydroxy-ellipticine, 9-aminoellipticine, 2-methyl-9-hydroxy-ellipticinium acetate are all cytotoxic and mutagenic, although 9-aminoellipticine has only marginal mutagenicity. They have also found that the latter compound intercalates only weakly and may instead exert its mutagenic activity primarily (or exclusively) by forming a covalent adduct with DNA. On the other hand, ellipticine, 9-methoxyellipticine, 9-hydroxyellipticine appear to cause frame-shift mutations by both intercalation and covalent binding with DNA. Paoletti concludes that:

a. the various ellipticines do not all interact with identical DNA sequences in the various strains of Salmonella.
b. only a small portion of the frame-shift mutagenicity shown by most ellipticines is due to simple intercalation.
c. there is no obvious correlation between mutagenicity in vitro and antitumour activity in vivo.

In animals, it is likely that most of the hydroxylated

pyrido[4,3-b]carbazole administered is excreted in the urine as conjugates (80). In cell culture, however, it has been shown that 9-hydroxyellipticine is much more cytotoxic and mutagenic than ellipticine itself, and has the highest affinity for DNA.

Paoletti has also shown that the antitumour activity exhibited by 2-methyl-9-hydroxyellipticinium acetate when tested against L1210 leukeamia implanted in mice is only second to that exhibited by ellipticine; whilst its cytotoxicity in L-1210 leukaemia cells is lower than that of 9-hydroxyellipticine (81). Subsequently, this compound has been developed by the French company S.N.O.F.I. as a soluble form of the anticancer agent.

It should also be noted that the 9-aminoellipticine used in Paoletti's work originated from the laboratory in Bath and was synthesized by Sainsbury and Webb in 1973. Regretably, this fact has never been acknowledged by the French workers.

Paoletti et al. have also found that ellipticine and its 9-substituted derivatives bind to the heme iron atom of cytochrome P-450 and thus inhibit microsomal monooxygenase (75). Consequently, 9-hydroxyellipticine has been shown to be a potent inhibitor of a wide variety of mutagens that require metabolic activaton, suggesting its usefullness in treatment for accidental exposure to chemical carcinogens (82).

Very recently, Archer et al. (33) described the

biological activities of three ellipticine derivatives, **99-101**, against murine P388 lymphocytic leukaemia in mice (Figure 20). Results showed that the 5-hydroxmethyl derivative **99** and ellipticine **1** were about equally potent whilst the corresponding carbamate **100** and ester **101** were both significantly more cytotoxic and antitumour active, particularly the carbamate.

The pharmacological properties of some pyridocarbazole analogues of ellipticine have also been reported and should be briefly mentioned. Bisagni *et al.* have synthesized a series of ellipticine and olivacine derivatives with various lipophilic and hydrophilic side chains attached at the C-1 position, as well as their 9-aza analogues (57,83-84) (Figure 21).

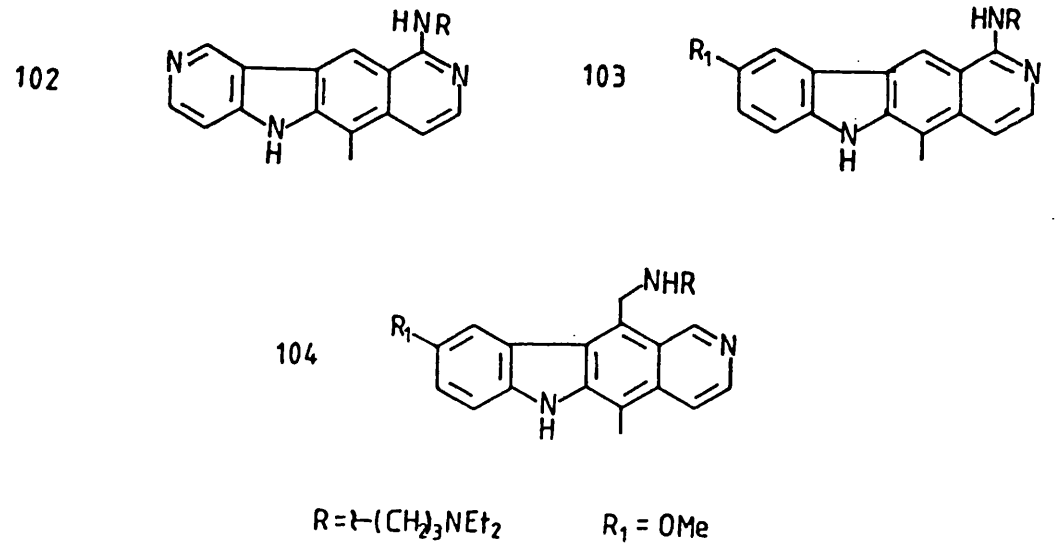


Figure 21

When tested on the L-1210 leukaemia system, the diamine **102** and **103** were said to exhibit cytotoxic and antitumour properties. In addition, demethylation of the latter compound at C-9 served to increase its cytotoxic, but did not change its antitumour activity. Interestingly, the presence of the various side chains at the C-1 position (except for 3-N',N'-diethylaminopropylamino) did not improve their anticancer effect compared to ellipticine and sometimes led to inactive compounds. In the case of the C-11 derivative **104**, it was found to have some cytotoxicity but weak antitumour activity.

Roques *et al.* (85-87) have investigated the relationship between DNA binding affinity and the cytotoxicity of a number of the angular pyridocarbazoles **105-106** where the pyridine atom is located at various positions in ring D (Figure 22). Although the binding affinities of these compounds are comparable to those of the [4,3-*b*] series, their cytotoxicty measured against L-1210 leukaemia cells *in vitro* differs significantly. The cytotoxicity of the first series was low compared to ellipticine whilst that of the second group was much lower. Interestingly, when the "dimers" (these are products of two identical monomers linked together by a spacer at the pyridine nitrogen site) of the ellipticine type **107** and of the angular isomers **108** were compared, the former was said to have insignificant antitumour activity, but the latter were claimed to be highly active. It was also pointed

out that a rigid spacer, e.g. of the bipyridyl type was necessary in order to produce active compounds.

The above observations clearly suggest that any direct comparison between the activities of ellipticines and their various analogues should be treated with great caution.

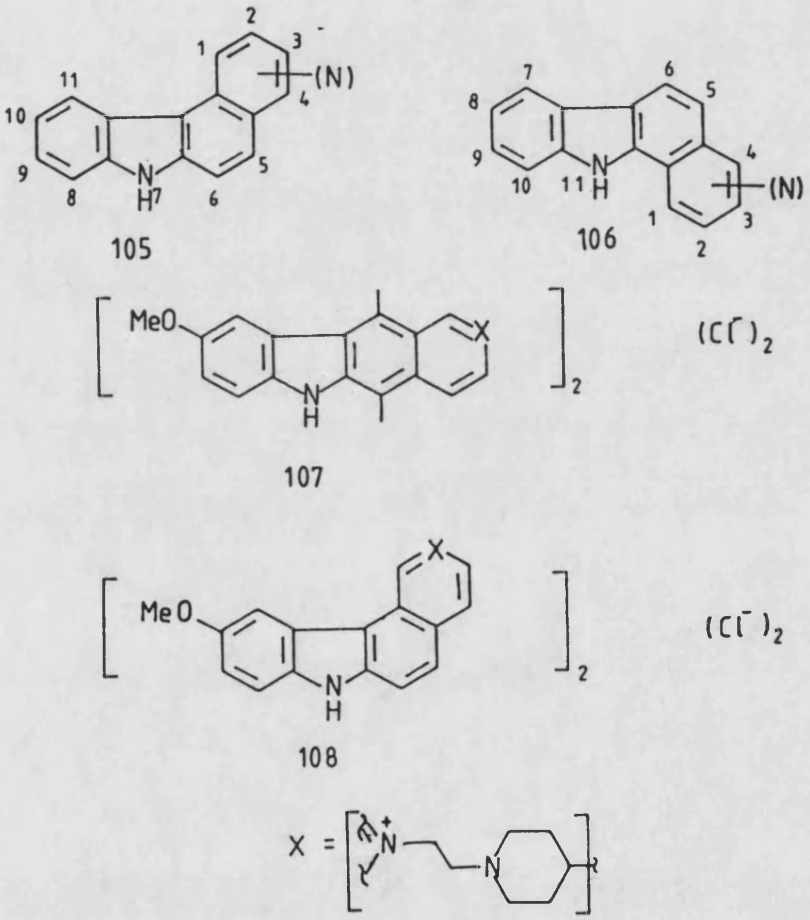


Figure 22

2.2 Mechanism of action of ellipticines

The mechanism of action of ellipticine *in vivo* and its derivatives is still not well understood, despite the fact that a great deal of work has been carried out on the problem (16). In recent years, some progress has been made, however, and various new hypotheses have been proposed. Considerable pharmacological evidence supports the view that DNA is a critical cell target for ellipticine, but still leaves the following questions to be answered:

1. Does the drug react with a replicative enzyme or protein, DNA polymerase, RNA polymerase, topoisomerase (e.g, DNA gyrase), or helix destabilizing protein or directly with the nucleic acid template itself?
2. Does the drug require specific activation, reduction, oxidation, or protonation, and if so at what positions?
3. Does it require a co-factor such as metal ions or an oxygen molecule?

It is now generally accepted that the pharmacological activity of ellipticine can be interpreted by more than one mode of interaction. These are described in the following

sections.

2.2.1 DNA affinity of ellipticine

It is believed that the antitumour activity of ellipticine and its derivatives is in part related to their high DNA binding affinity (88). Many of them bind to doubly stranded DNA with an affinity coefficient of 10^{-5} to 10^{-6} M (88). However, no correlation between their antitumour activity and DNA binding affinity has been established. There are many derivatives having nearly the same DNA binding constants which have been found to be either less or not active when compared to ellipticine itself (16,85). More than one form of binding relationship is possible. Intercalative and covalent binding are the two major contenders and these are discussed in separate sections below, but there could also be reversible non-intercalative interactions on the outside grooves of DNA (89).

The efficiency of intercalative binding can vary depending on the presence of additional functional groups; as stated earlier, it has been found that the addition of an amino, hydroxy or methoxy group at C-9 leads to a ten-fold increase in the DNA binding constant (88), presumably due to hydrogen bonding with two base pairs. It has been suggested that the hydroxy group of 9-hydroxyellipticine can also interact with the phosphate sugar backbone through hydrogen bonding leading to a generalised affinity between the two

molecules rather than a site specific one (85).

2.2.2 Intercalative binding of ellipticine to DNA

A wide variety of polycyclic molecules are known to bind to DNA by intercalation (90). Some of these, including actinomycin (91) and daunomycin (92-93), have essential side chains whereas others, including proflavin and ethidium do not. These latter molecules may be considered to be "simple" intercalating agents and are distingushed by a tendency for lower binding strengths, faster kinetics of reaction and dissociation (94), and less specificity for binding to helical DNA. The two groups differ in their effects on the synthesis and processing of RNA in L1210 cells. Ellipticine was found to resemble the simple intercalators proflavin and ethidium in this regard (95).

Waring et al. have reported that ellipticine increased the viscosity and decreased the sedimentation coefficient of native calfthymus DNA (96). Waring also established that the plane of the ellipticine ring system is orientated parallel to the plane of the bases of the DNA. Experiments with circular DNA showed that the binding of ellipticine results in a local unwinding of the double helix as required by the intercalation hypothesis. This suggestion of an intercalative mechanism of binding was further supported by ^{1}H n.m.r. studies (97) and a X-ray analysis on a co-crystallized mixture of ellipticine and 5-iodo-

cytidylyl-(3'-5')-guanosine (98). The crystallographic studies also reveal that the size and shape of the 6H-pyrido[4,3,b]carbazole ring lead to an almost perfect overlapping of the aromatic ring with that of a DNA base pair, an ideal situation for intercalative binding. Anticancer activity and the cytotoxicity of intercalative agents generally are associated with interference in at least some aspects of transcriptional, and replicative processes, as well as with gross DNA damage and consequent misrepair (99-100). However, in practice, it is not certain as to what extent the antitumour activity can be accounted for by the intercalative interaction.

Waring et al. have suggested that the basicity of ellipticine may have an important bearing on its action on cells (96). They noted that when bound to DNA, ellipticine may be in its cationic form, the positive charge being favored by the negative charge of the macromolecule. Thus, the extent of binding to DNA may depend on intracellular pH (96). There is some evidence to suggest that cancerous and normal cells have different pH, but this is not proven (101).

2.2.3 Covalent binding of ellipticine to DNA, RNA, protein and amino acid

Paoletti et al. (102) have put forward the view that, in vivo, a biotransformation occurs (Figure 23). This states

that 9-hydroxyellipticine and the corresponding ellipticinium salt **95** undergo two stepwise single electron oxidations in the presence of peroxidase to give the phenoxy radical **109** and the quinone imine **110** respectively.

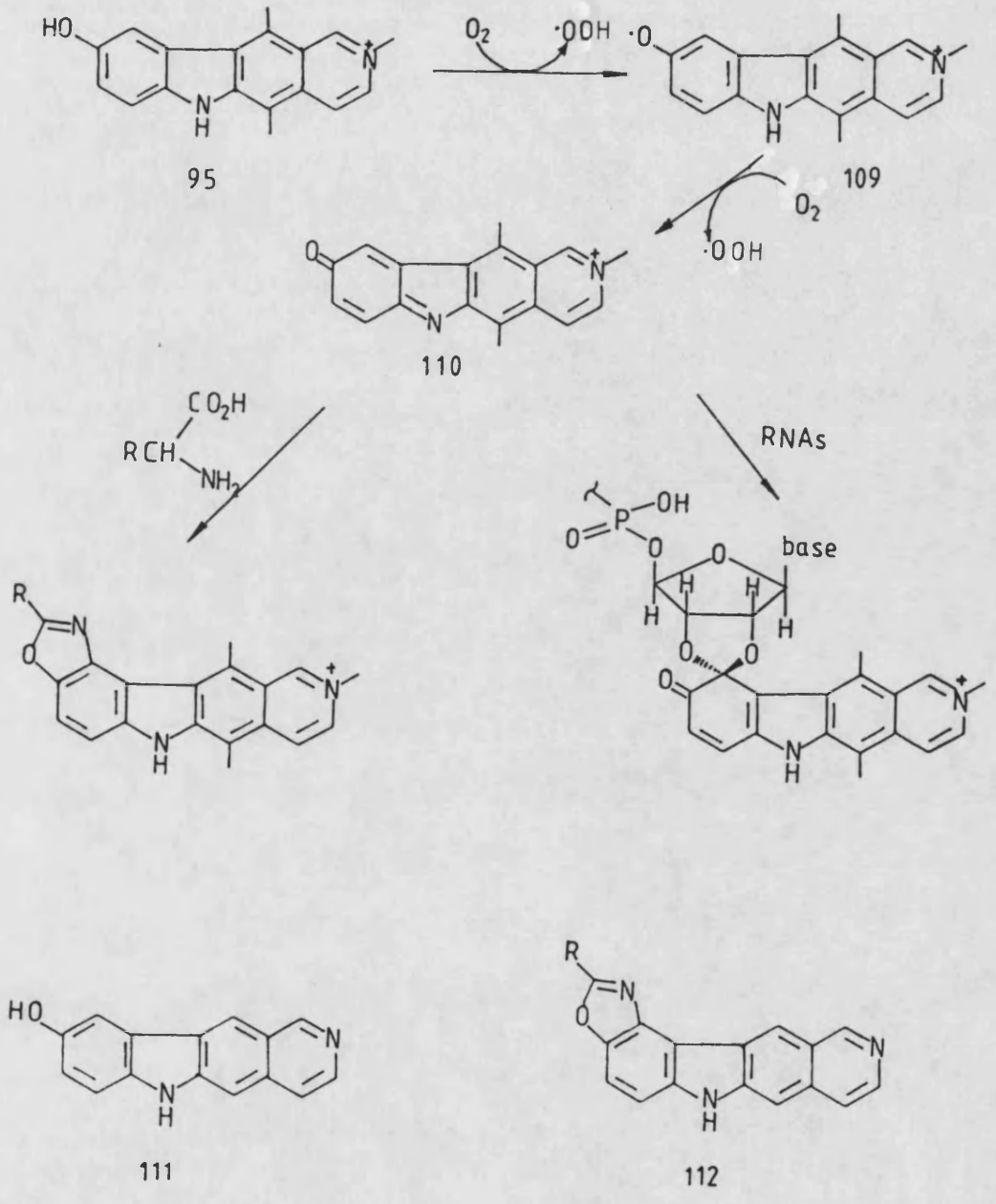


Figure 23

The latter is strongly electrophilic and therefore would be expected to covalently bind to biomolecules, such as proteins and nucleic acids. The iminoquinone **110** has been made *in vitro* and under chemical or biochemical conditions, undergoes addition reactions with various compounds such as amino acids (103), ribo-nucleosides and nucleotides (104-107). Based on these findings, Potier *et al.* propose that the antitumour activity of this class of compound could also be explained on the basis of alkylation at the terminal end of t-RNA to stop the formation of aminoacyl t-RNA, and at the end of poly-A-tail of the m-RNA or the "cap" that is present at the 5'-end of m-RNA. Any of these events might thus inhibit the biosynthesis of proteins. Recently, Dugue *et al.* have discovered that incubation of 9-hydroxy-2-methylellipticinium salt **95** with L1210 murine leukaemia cells at 37 °C for eight hours results in covalent binding of the drug to both DNA and RNA, but not to proteins (108).

However, despite all the above findings, the validity of the various hypotheses has recently been challenged by Archer *et al.* (33). He has shown that the desmethyl 9-hydroxypyridocarbazole **111** is inactive against murine P388 lymphocytic leukaemia. The absence of the methyl groups does not, however, prevent oxidation to an iminoquninone which will then react with an amino acid to give **112**, so Archer concludes this intermediate **110** is not the key to activity and alternatively, he proposes that ellipticine is,

as before, transformed to the 9-hydroxy derivative **16** (Figure 24). This species, in turn, is enzymically converted first into the hydroxymethyl compound **113**, which is then further transformed to **114**. The latter derivative now prosesses a good leaving group, and functions as an alkylating agent for macromolecule such as DNA etc. to give products of the general form **115**. This theory is supported by the much enchanced antitumour activity of the carbamate **99** as compared to ellipticine and the carbinol **100**.

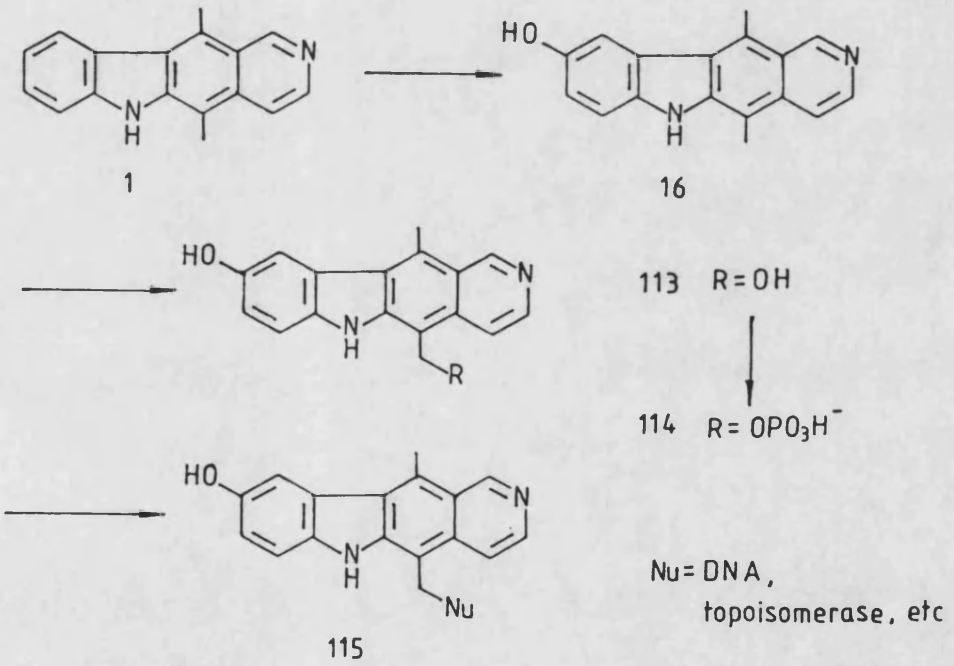


Figure 24

2.2.4 Single DNA strand breaks by ellipticine

Pommier et al. has demonstrated that when 9-hydroxyellipticine is incubated with L1210 cells at 37°C for one hour, single and double strand DNA breaks occur in a reversible manner (109). Similarly, Dugue et al. suggested that both DNA strand breaks and covalent binding may be responsible for the cytotoxicity of ellipticine (108). Ross has pointed out that ellipticine causes a higher frequency of DNA strand breaks than does adriamycin, yet it is far less cytotoxic. He suggests that ellipticine-induced breaks are rapidly repaired when the drug is removed from the surrounding medium whereas adriamycin-induced breaks are retained much longer (110).

Three distinct kinds of single strand breaks are recognizable (111) and they are due to:

1. direct attack by free radicals,
2. DNA phosphotriester formation and hydrolysis,
3 base alkylation, depurination or depyrimidination, and subsequent hydrolysis of the adenosinephosphate site.

Type 1 effects are commonly associated with quinone type antibiotics. Paoletti has already suggested that the phenoxy radical generated by the action of peroxidase, could be considered responsible for single DNA strand breaks caused by various hydroxyellipticines (112). It is thought

that in the course of oxidising 9-hydroxyellipticine to the phenoxy radical, an oxygen molecule is reduced to a reactive "superoxide ion" which then reacts with water to give a hydroxyl radical. The latter is highly reactive and can easily cause DNA strand breaks. This argument is dependent on the validity of the "iminoquinone mechanism" (Figure 23) which as already mentioned, is doubted by Archer. On the other hand, if these free radicals are involved in the damage of DNA, they shall also initiate lipid peroxidation as observed in the case of the quinone type antibiotics. Thus further work is required for the charactisation of the cause of single strand breaks that is associated with ellipticine adminstration.

2.2.5 DNA double strand breaks by ellipticine (involving DNA topoisomerase II)

The recent demonstration that the nuclear enzyme DNA topoisomerase II mediates DNA scission in cells exposed to intercalative anticancer agents creates important new opportunity for understanding how the drugs work (109). Regulation of DNA topology is of critical importance to normal cellular function, and one of the principal means by which the cell accomplishes this is by DNA topoisomerases I and II (113-115). Both of these nuclear enzymes occur in all living cells although more is known about mammalian topoisomerase II than topoisomerase I. There are really two

components to the action of topoisomerase II. The first is the ability to concurrently and reversibly cleave both strands of doubly stranded DNA, and the second is its "strand passing" activity which facilitates the formation and deformation of the supercoiling structure of DNA (114-115). The first indication that DNA topoisomerase II might be involved in the action of anticancer agents came from studies of adriamycin and ellipticine by Ross et al. (116-117). In the presence of these intercalating agents, the cleavable complex formed between the DNA and the enzyme fail to reseal, resulting in DNA double strand breaks. Although little is known about the mechanism of this action, it is established that intercalation mode of DNA binding is not a pre-condition for the process (118). In fact, a different class of antitumour agents, the epipodophyllotoxins have been shown to inhibit strand passing activity and potently induce DNA cleavage by topoisomerase II in vitro (119-120). This suggests that the drug might elicit its action via some form of interaction with the enzyme. Interestingly, Pommier et al. have reported that amsacrine (m-AMSA) stimulates the protein-associated DNA strand breaks at all concentrations, whereas 2-methyl-9-hydroxyellipticium acetate stimulates cleavage at low concentrations and inhibits the effect at high concentrations (121). Ross argues that by creating topological distortion in DNA, by extensive intercalation, enzyme recognition of DNA binding site is interfered with,

thus disfavoring the DNA double strand breaking process mediated by Topoisomerase II. The question is: how then, does a higher concentration of amsacrine, another effective intercalator, not similarly inhibit topoisomerase II mediated double strand breakage?

The mechanistic studies of the antitumour activity of ellipticine have been significantly promoted to a higher level since the recent identification of topoisomerase II as a probable intracellular target. It is now imperative to determine how the drug influences the properties of this enzyme.

Section III

Results And Discussion

3.1 Basis of the project

It is acknowledged (67,122) that the poor water solubility of the ellipticines has been a major drawback in their widespread acceptance as clinically useful drugs. For instance, Paoletti et al. (123) terminated a human clinical study with 9-hydroxyellipticine (which is known to be one of the most active in the series) simply because insufficient doses of the drug were translocated from the injection site to the tumour (122).

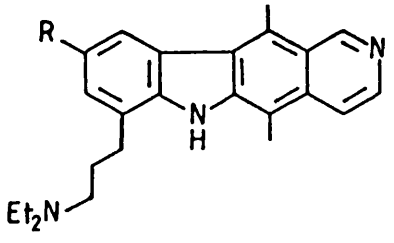
While studies of the pharmacokinetics of these antitumour agents within the body have been few (68), it has been demonstrated that those which do not bear a polar substituent (e.g. ellipticine and 9-methoxyellipticine) bind strongly to acidic lipids (124-125) and therefore remain relatively longer in the lipid layers of the cell. This so-called depot effect leads to prolonged interaction with certain enzymes at the microsomal membrane and, also, causes changes in membrane permeability. Together, these features may lead to cell death. Less lipid-soluble ellipticines, e.g. 9-hydroxy- and 9-amino-ellipticine, are adsorbed on the membrane surface and in this way discouraged from penetrating the membrane and reaching the nucleus of the cell where DNA occurs (126).

In this respect, it seems that a balance needs to be struck between lipophilicity and hydrophilicity. One possibility would be to introduce an alkyl chain tipped with

an amino group onto the ellipticine nucleus and this has the important feature that the polar group is isolated by the alkyl chain from the π-system of the tetracycle (direct substitution of polar groups onto the nucleus usually leads to a reduction of anticancer effect). In the ellipticines, there are eleven potential anchorage points for the chain. Computer modelling work with ellipticine models intercalated within the DNA base pair pocket suggested that substituents emanating from C-5, C-7 and C-8 do not seriously clash with the sugar-phosphate backbone of the nucleic acid (127-128). In this work, the objective was to investigate syntheses of 7- and 8-substituted ellipticines while my colleague, Andrew Ratcliffe in a separate project (55), considered routes to C-5 analogues.

3.2 Synthetic work towards 7-substituted ellipticine

3.2.1 Attempts to synthesise the ellipticine 116 using the Sainsbury-Weerasinghe route



116 R = H

117 R = OCH_3

Our intended targets were the 7-substituted ellipticines 116 and 117. Several 7-substituted

ellipticine derivatives, such as 7-chloro- **65**, 7-fluoro- **66** and 7-methyl-ellipticine **67** have previously been prepared (53) by the Sainsbury-Weerasinghe route (Figure 15). Our plan was to use this route to prepare the pyridocarbazole **116** and first to condense the aldehyde **60** with the appropriate o-substituted arylhydrazine **118** in order to provide the hydrazone **119**. Through the implementation of a Fischer indolisation reaction, this hydrazone would then form the pyridylindole **120** and in several further steps, the structure of the ellipticine **121** could be built up and converted by reduction into the target compound **116** (Figure 25).

Accordingly the aldehyde **60** was synthesized by a method (55) regularly employed in this laboratory. A Wittig-Horner reaction between 3-acetylpyridine **26** and the activated phosphonoester **122** gave the unsaturated ester **123**, and this product was reduced by catalytic hydrogenation to yield the ester **124**. Reduction of this with lithium aluminium hydride in tetrahydrofuran afforded the alcohol **125** which was then oxidised by the Swern technique to furnish the aldehyde **60** (Figure 26).

Next we attempted to prepare the hydrazine **118** (Figure 27). Thus o-nitrocinnamic acid **126** was first converted to the amide **127** *via* its acid chloride. The crude product was directly reduced over palladium on charcoal to afford the aniline **128** in good yield.

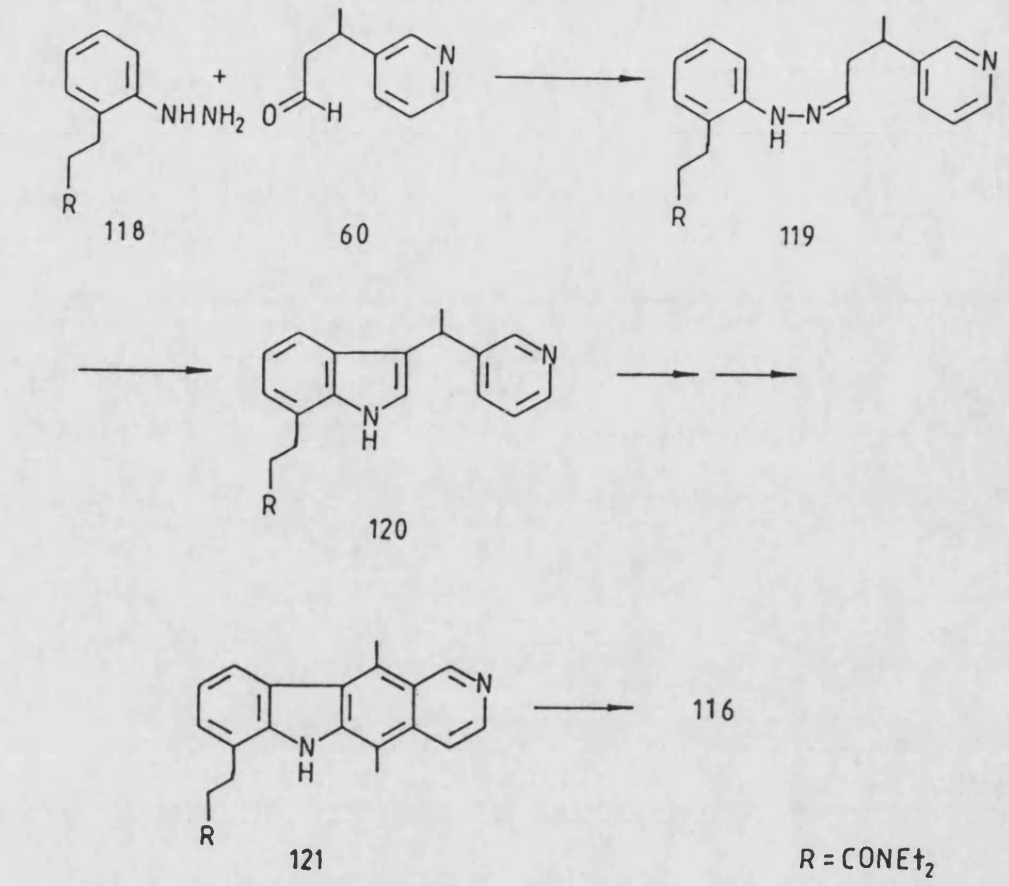


Figure 25

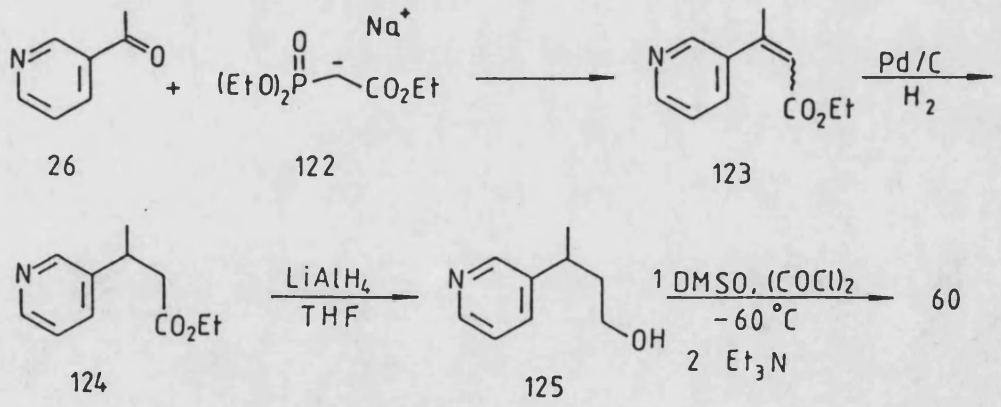


Figure 26

Unfortunately, attempts to convert the latter compound to the corresponding hydrazine **118** have all failed. For example, when the aniline **128** in an hydrochloric acid solution was diazotised with sodium nitrite under normal conditions (129), it gave an orange solution. Treatment of this solution with sodium sulphite did not result in formation of the hydrazine **118**; instead the phenol **130** was produced. This suggests that the diazonium salt **129** has been formed, but did not undergo reduction by the action of sodium sulphite. In a separate attempt, the aniline **128** was again diazotised and now was treated with tin(II) chloride. An exothermic reaction occurred and a thick

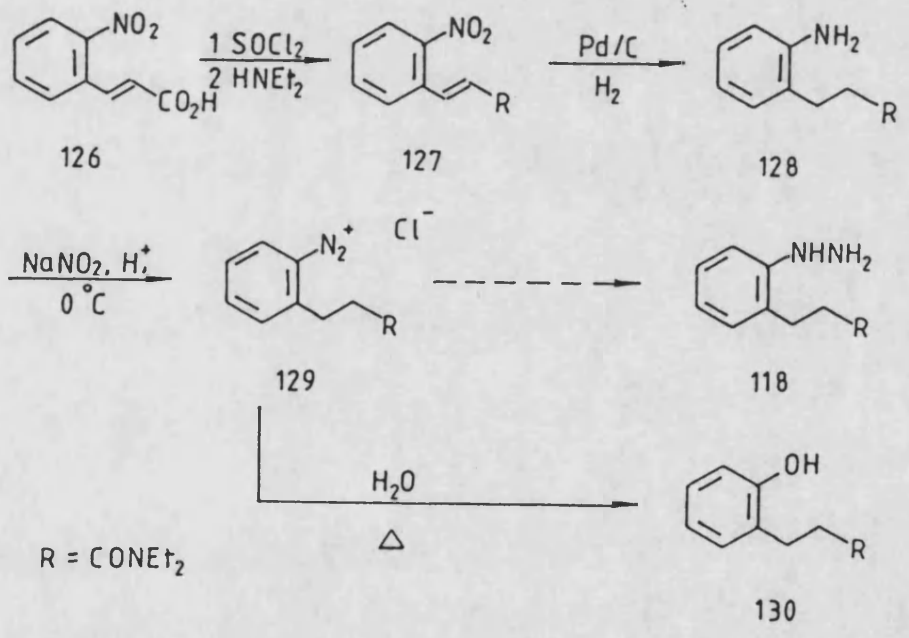
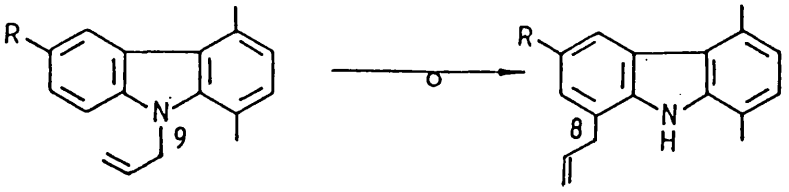


Figure 27

suspension was formed immediately. The precipitated solid was collected, but this on treatment with base gave only a dark tarry product which we could not characterise. Facing the difficulty of obtaining the o-substituted phenylhydrazine **118** at the beginning of a multi-stage synthesis, we decided that an alternative route to our ellipticine targets was necessary.

3.2.2 The synthesis of carbazoles functionalised at C-8

The modified Cranwell-Saxton synthesis (Figure 17) is known as an efficient means of entry to some ellipticine compounds, e.g. **96**- **98** (Figure 20). The key step in the approach being the formation of 1,4-dimethylcarbazoles **75** from the corresponding indoles **73**. We were interested in adapting this strategy as the route towards our targets and thus we needed to devise a preparation of the appropriately C-8 functionalised carbazoles. It was originally anticipated that a C-8 substituent would perhaps be introduced regio-selectively into the 1,4-dimethylcarbazole system *via* rearrangement reactions of the N-allylcarbazoles **131** and **132** (Figure 28). Although such a transformation has not been demonstrated previously with carbazoles, a similar reaction of N-allylindole **135** is known (130). Here the product is 3-allylindole **136**, but the rearrangement is thermally induced and requires pyrolysis of the indole **135** at 470 °C (Figure 29).

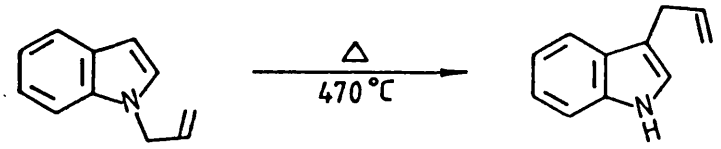


131 R = H 133

132 R = OMe 134

Figure 28

Of more practical importance is the report by Kazaki et al. (131) that the same transformation can be achieved under a milder condition by treating the N-allylindole **135** with various Lewis acids. These include zinc chloride, titanium tetrachloride and antimony pentachloride, but the most effective is aluminum trichloride.

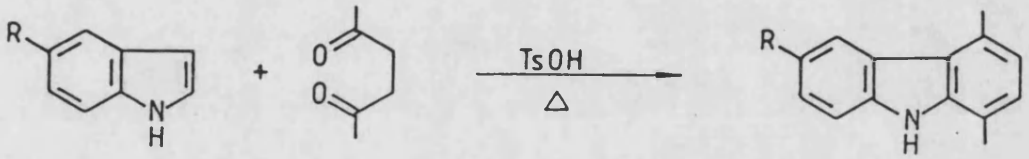


135 $AlCl_3$, 80°C, C_6H_6, 2h, 58% 136

Figure 29

We decided to investigate this rearrangement chemistry with 9-(N)-allyl-1,4-dimethylcarbazole **131** which was readily prepared in two steps: indole **25** was allowed to

react with hexa-2,5-dione **74** in the presence of 4-toluenesulphonic acid monohydrate to give 1,4-dimethylcarbazole **24**. This product was then N-allylated using sodium hydride and allyl bromide (Figure 30). An attempt to thermally rearrange the N-allylcarbazole **131** failed and the starting material remained largely unchanged after being heated in xylene for 30 h under reflux. Next the reaction was repeated in dichloromethane at room temperature using aluminum trichloride as catalyst and after 9 h, two products were formed in roughly equal amounts.



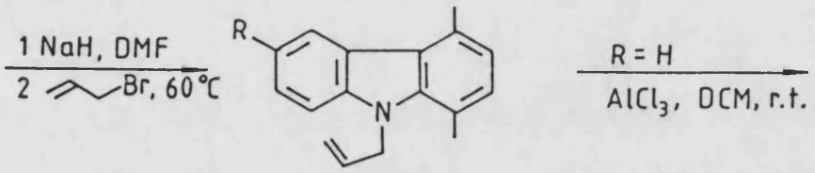
25 R=H

137 R=OMe

74

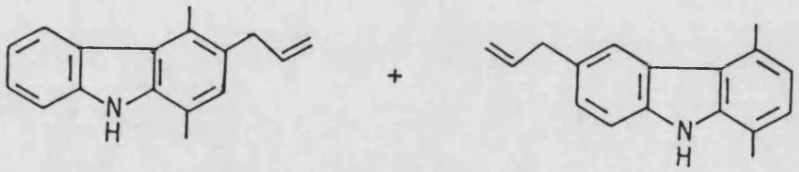
24 R=H

138 R=OMe



131 R=H

132 R=OMe



139

140

Figure 30

They were assigned as the two isomeric products **139** and **140** and the locations of the allyl groups in the two compounds were deduced from ^{1}H n.m.r. spectroscopic data and later confirmed by nuclear Overhauser experiments. In the spectrum of the 3-allyl isomer **139**, the methylene protons of the allyl group give rise to a multiplet at 3.6 ppm, which if irradiated causes enhancements of intensity of the resonance of the C-4 methyl protons (at 2.8 ppm) and that of H-2, a singlet at 7.0 ppm. A second irradiation was carried out on the C-4 methyl resonance at 2.8 ppm and this resulted in enhanced signals at 8.2 ppm (H-5) and at 3.6 ppm (the signal of the allylic methylene protons). Irradiation of the second methyl resonance at 2.5 ppm caused an enhancement of the intensity of the 1H resonance at 7.0 ppm due to H-2, but did not affect any other aryl proton signal. These results thus conclusively show that the carbazole is substituted by an allyl group at C-3. In the case of the other isomer **140**, assignment of the ^{1}H n.m.r. signals follows by comparison with those made for 1,4-dimethylcarbazole **24** and for the 3-allylated compound **139**. For example, as is general in such compounds, the signal due to the H-5 proton occurs at lowest field of all of the aryl proton resonances while those due to H-7 and H-8 coincide to give a multiplet at <u>ca</u>. 7.2 ppm. In a nuclear Overhauser experiment, irradiation of the methylene protons signal in this compound (at 3.8 ppm) produced an enhancement of intensity in both the H-5 signal (at 8.1 ppm) and in the multiplet (at

7.2 ppm) due to the resonance of H-7 (and H-8). We presumed that the formation of these two products arose from two consecutive [3,3]-sigmatropic processes, i.e. an aza-Cope first, followed by a Cope rearrangement (see also p.66-67) (Figure 31). As a result, these products are expected, but we were surprised that none of the 8-allylcarbazole **133** had formed. We then turned our attention to the 6-methoxylated carbazole **132** since in this case, the 6-position is now occupied by a methoxyl substituent and the required 8-allylated compound **134** should now be available through an analogous rearrangement reaction.

The N-allylcarbazole **132** was prepared from 5-methoxyindole **137** and hexa-2,5-dione **74** in the usual way, and the product **138** N-allylated using sodium hydride and allyl bromide. The indole **137** was itself prepared according to a procedure recommended by Lloyd *et al.* (132); in which the *o*-nitrotoluene **141** is condensed with tripiperidinomethane under thermal condition to give the piperidinostyrene **142**. Without purification, the latter was directly transferred to a bufferred (ammonium acetate) solution of titanium(III) chloride with the aid of acetone as a solvent. Under this condition, the nitro group was immediately reduced *in situ* by the action of titanium(III) chloride to give an amine **143**. This compound in turn afforded the indoline **144** *via* an intramolecular nucleophilic attack of the amino group at the β-position of the styrene. Elimination of piperidine from the indoline

took place in the same pot to furnish the required indole 137 (Figure 32).

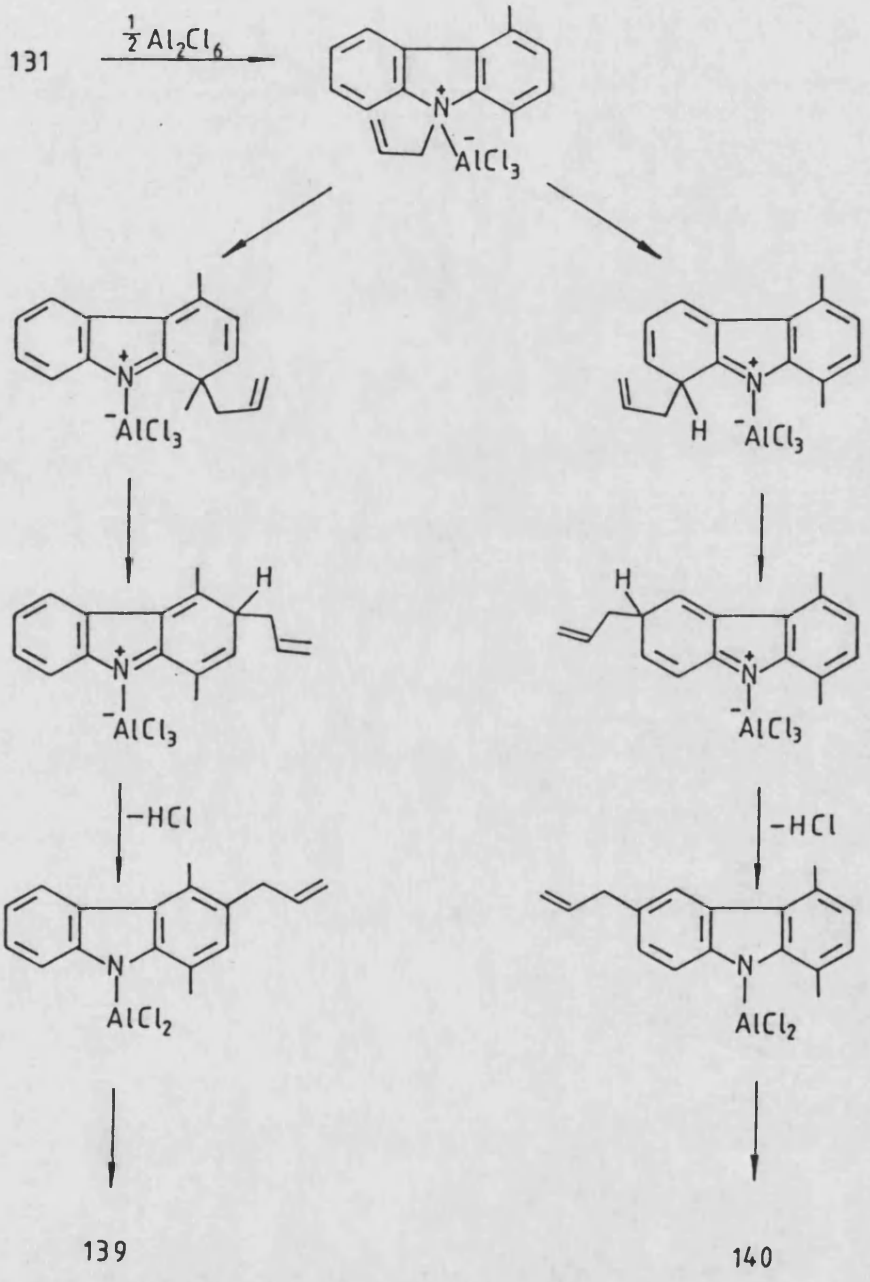
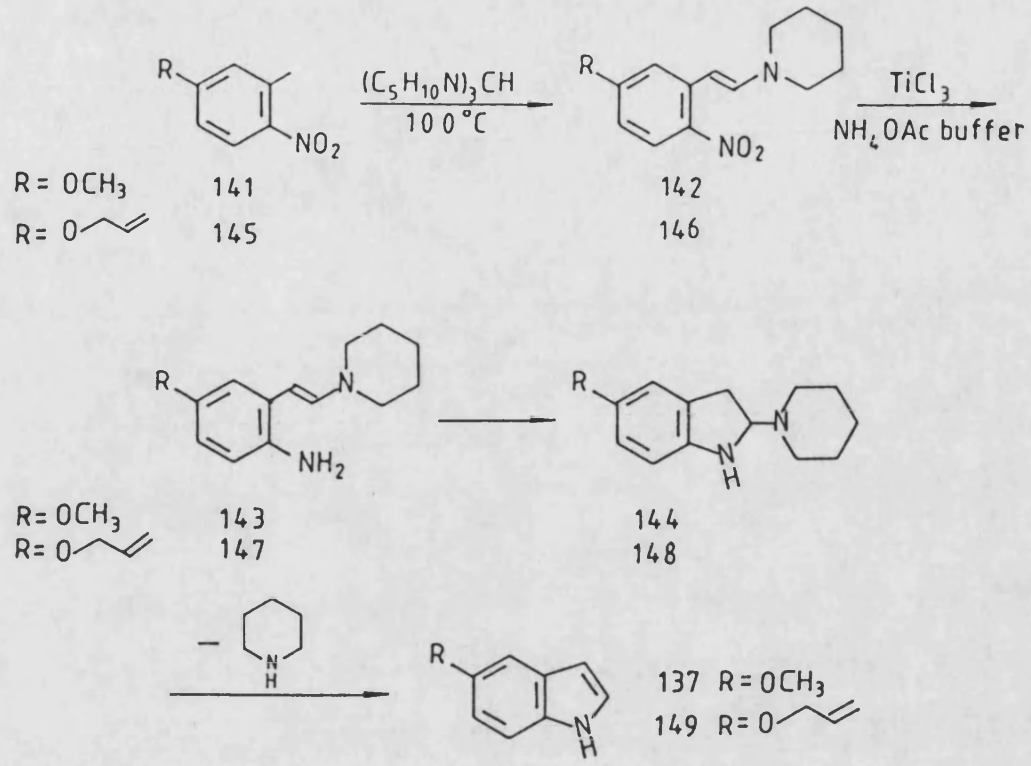
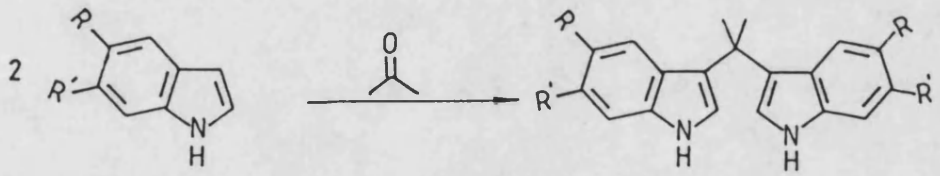


Figure 31



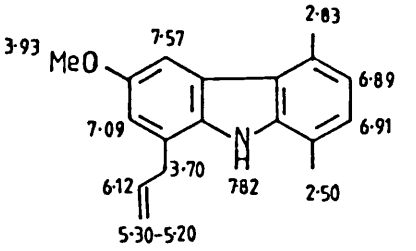


137	R = OCH_3 R'= H	152
150	R = O– R'= H	153
151	R = H R'= OCH_3	154

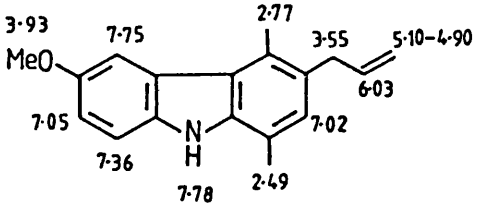
Figure 32

In our hands, another product was also obtained in this reaction and this was identified as the bis-indolylpropane **152**. A similar product **154** has also been isolated by another worker (133) in this group when he prepared 6-methoxyindole **151** using the same procedure. These bis-indolyl products arise from a side reaction between the desired indoles and the acetone that is recommended as a co-solvent in the experiment; however, no mention of the formation of these rather obvious products was given in the original reference. The problem is simply avoided when acetone is replaced by tetrahydrofuran as the transfer solvent.

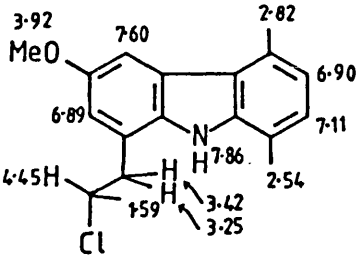
The condensation reaction between the methoxyindole **137** and hexadione **74** was then carried out and the conventional extractive work-up was replaced by the use of column chromatography. In this way, the whole procedure could be simplified and loss of product minimised. The allylcarbazole **132** was next heated under reflux in xylene for 24 h, but the starting material remained largely unchanged. In contrast, when it was treated with aluminum trichloride in dichloromethane, all starting material was consumed after 7 h. Usual work-up procedure then gave three products which were isolated in 62%, 24% and 9% yield respectively. The structures of these compounds were established as the carbazoles **134**, **155** and **156** respectively (Figure 33).



134



155



156

Figure 33

In the ^{1}H n.m.r. spectrum of the 8-allylcarbazole **134**, two doublets at 6.91 and 6.89 ppm are quite typical of the H-2 and H-3 signals of 1,4-dimethylcarbazoles. Obviously then, the 2- and 3-positions remain unsubstituted in this product. Two additional doublets at 7.57 and 7.09 ppm, each has a coupling constant of $\underline{J}$=2.4 Hz, indicative of a "<u>meta</u>" relationship and are therefore assigned as the resonances of H-5 and H-7. By way of contrast, the ^{1}H n.m.r. spectrum of the 3-allyl isomer **155** exhibits a standard first order AMX pattern for resonances of the aryl protons of ring A at 7.75(d), 7.36(d) and 7.05 ppm (dd). These resonances resemble those of the parent and are assigned to the signals of H-5, H-8 and H-7

protons respectively. The one remaining aryl proton signal at 7.02 ppm appears as a singlet and is due to the resonance of the H-2.

The presence of a chlorine atom in the third product **156** is evidenced by its mass spectrometric data. For example, the molecular ion appears as two peaks at m/z 301 and 303 in the ratio 3:1; this is to be expected for the natural abundance of the chlorine isotopes. The ^1H n.m.r. spectrum of the chloro compound also resembles that of the 8-allylcarbazole **134** except that it does not reveal the characteristic spin-spin pattern for the resonances of an allyl group. Instead, there is now a 3H doublet at 1.59 ppm, a pair of 1H double doublets at about 3.25 ppm and a 1H multiplet at 4.43 ppm. These data are consistent with the presence in the molecule of a $CH_2CH(Cl)CH_3$ group located at C-8. Results from decoupling experiments also affirmed this assignment.

Once again, aluminum trichloride was found to be the only effective Lewis acid among many tried in causing the rearrangement of the N-allylcarbazole. Ethyl aluminum dichloride, zinc chloride, boron trichloride and boron trifluoride etherate all had little effect on the N-allylcarbazole **132** even after long reaction times. Similarly, this substrate was unchanged after treatment with trifluoroacetic acid. We also observe that, with aluminum trichloride, the effect of solvent is crucial; reactions in non-polar solvents like toluene and 1,2-dichloroethane are

similar to those in dichloromethane and rearrangements to C-allylated products result. However, when nitromethane was employed, the course of the reaction changed completely; the starting material was deallylated within 45 min at 0°C to yield the simple carbazole **138**.

Although it was not our intended objective to investigate the mechanistic aspects of this rearrangement reaction, we were still interested to know if it was an inter- or intra-molecular process. Surprisingly, intra-molecular [3,3]-sigmatropic processes such as the aza-Cope rearrangements have not been reported in the case of carbazoles, but Fries rearrangements of acylated carbazoles and the equivalent aluminum trichloride mediated Friedel-Crafts acylations of carbazoles have been studied before (134). In fact, whether a Fries rearrangement is an inter-, intra-molecular or "between the two" process has long been an arguable subject (135-137). A photo-Fries process has been carried out by Ivanov *et al.* (138) on N-acetylcarbazole **157**. After irradiation of a solution of this substrate in isopropanol with ultra-violet light for just 80 s, the C-acylated isomer **158** was obtained (Figure 34). The course of this reaction is, however, solvent dependent and in cyclohexane, the two acylated carbazoles **158** and **159** were obtained in an equal molar ratio (139). In addition, a Fries rearrangement of N-acetyl-carbazole **157** has been reported by Yurev *et al.* (140). Here, the only product isolated was 3-acetylcarbazole **159**

in 63% yield and the conditions employed were nitromethane with 1 mol equivalent of aluminum trichloride at 60-90 °C. Interestingly, the same workers also reported a corresponding Friedel-Crafts type acylation (141) in which carbazole **160** in nitromethane was treated with acetyl chloride (2 eqv.) and aluminum trichloride (1 eqv.) at 90 °C for 5 min and a mixture of C- and N-acetylated products **157 - 159, 161** were obtained (Figure 35).

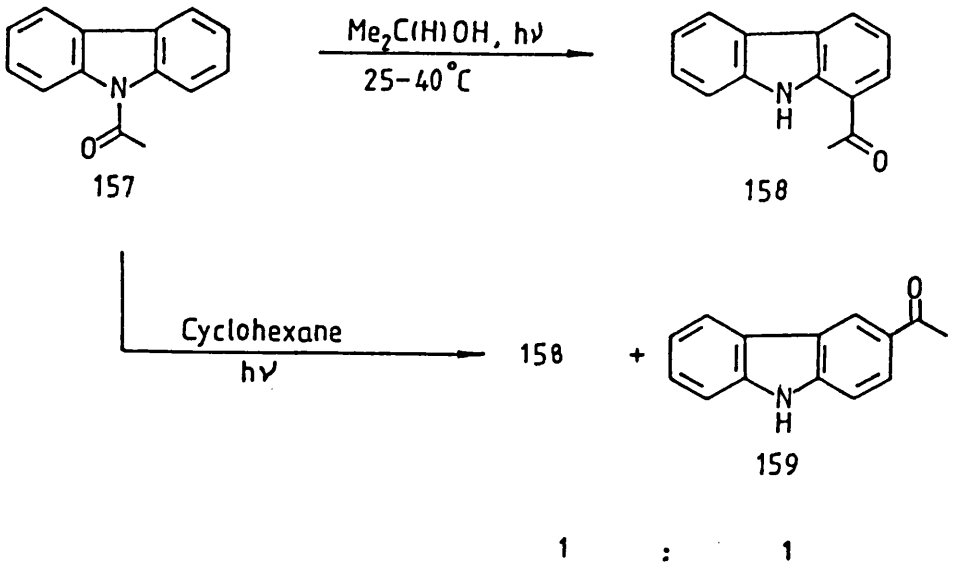


Figure 34

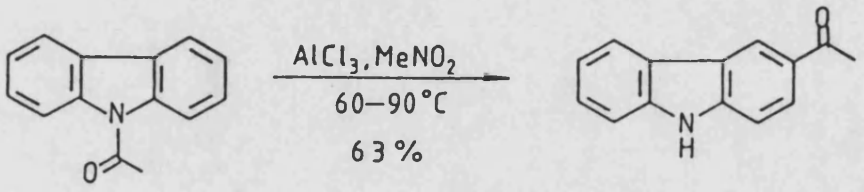
In order to make a judgement between inter- and intra-molecular rearrangements in the case of our N-allylated carbazoles, we designed a simple cross-over experiment in which equal amounts of the N-allylcarbazole **131** and its 6-methoxy-des-allyl derivative **138** were

treated together with 2 mol equivalents of aluminum trichloride. Three compounds were eventually obtained and were shown to be identical with the starting methoxycarbazole **138** and the two rearranged isomeric products **139** and **140**. The recovery of the unchanged methoxycarbazole **138** was 99% and no crossed-over products were observed. This result suggests our allyl rearrangement is an intramolecular process for if an intermolecular Friedel-Crafts type allylation had taken place, attack of the free allyl-aluminium chloride complex would have taken place preferentially with the methoxylated carbazole rather than with its less electron rich parent.

In light of the outcome of this cross-over experiment, we propose that the rearrangement processes we observe involve charge-induced intramolecular [3,3]-sigmatropic shifts. In the former case, an aza-Cope rearrangement onto the neighbouring 8-position provides the 8-allyl-6-methoxy-carbazole **134**, whereas an aza-Cope rearrangement onto the neighbouring 1-position, immediately followed by another Cope rearrangement provides the 3-allyl-6-methoxycarbazole **155**. Similarly, both of the isomeric products **139** and **140** in the des-methoxy series arise from stepwise aza-Cope and Cope rearrangements.

Although the term sigmatropic rearrangement was originally used by Woodward and Hoffmann for "uncatalyzed intramolecular processes", it has been widely employed in recent years to characterise many related reactions (142).

The expression "charge-induced" sigmatropic rearrangement was introduced after it was realized that many otherwise thermally mediated reactions will take place at ambient, or even at low temperature when an "inducing agent" is added. These agents include Lewis acids, transition metal catalysts and, sometimes, even strong Brønsted acids (142).



157 159

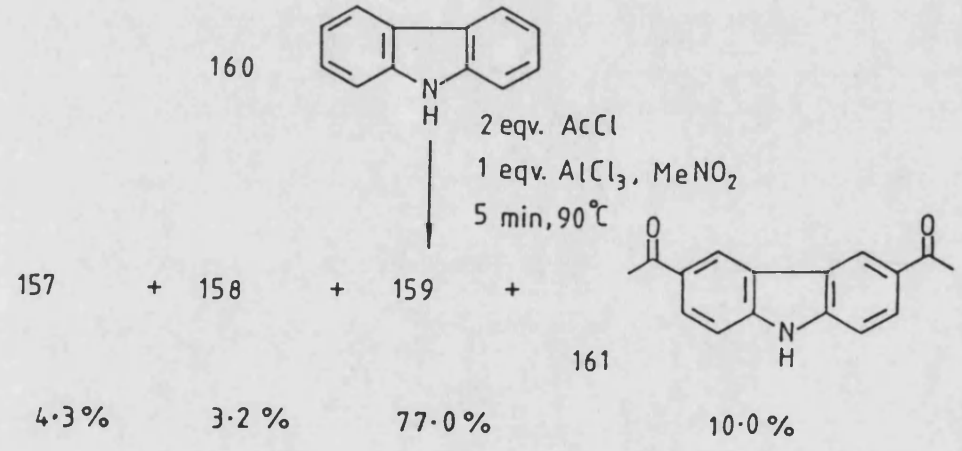


Figure 35

For example, Schmid et al. (143) established that boron trichloride is a suitable Lewis acid for aromatic

Claisen rearrangements (Figure 36). The amount of Lewis acid required in this case was, however, stoichiometric and therefore boron trichloride is not classified as a catalyst. Schmid et al. (144) have also extended their work into the analogous amino-Claisen series. In a typical experiment, the N-allyl aniline **162** was treated with 1.1 mol equivalents of zinc chloride in xylene under reflux for 4 h to give C-allylated products **163** and **164** in 8:1 (74.5% overall yield) (Figure 37).

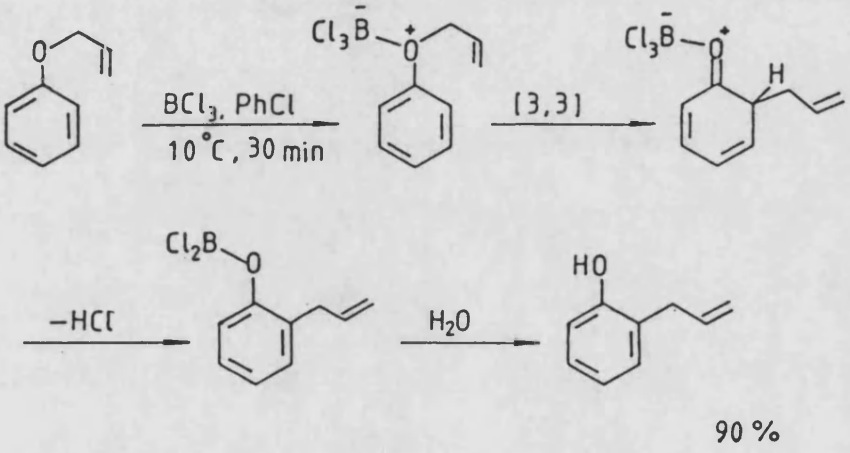
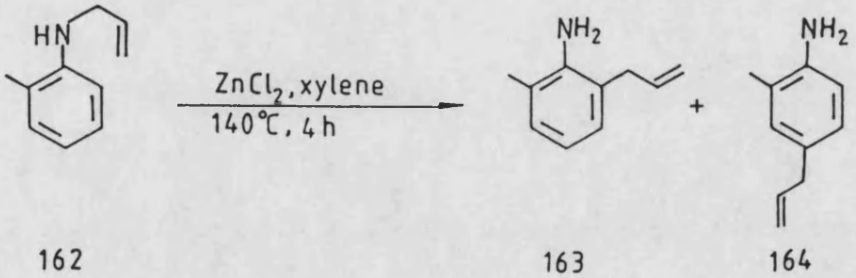


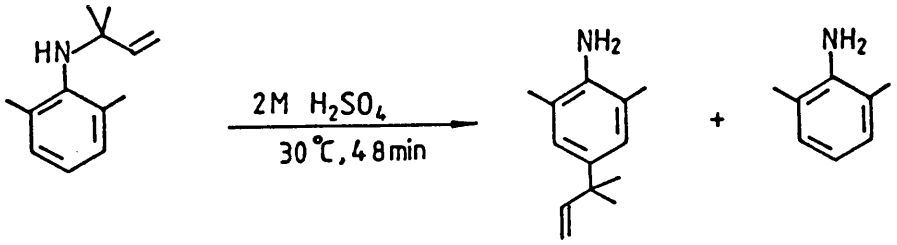
Figure 36



162 163 164

Figure 37

Hansen et al. (145) have shown that the role of zinc chloride was not unique in these processes and they found that by maintaining the amine **165** in 2 M sulphuric acid at 30 °C for 48 min, the 4-allylaniline **166** was obtained in 39% yield, alongside with a significant amount of the deallylated aniline **167** (21%) (Figure 38).



165 166 167

Figure 38

When the chloride **156** is treated with sodium hydride in dimethylformamide, the allylcarbazole **134** is regenerated. Two molar equivalents of base were used for this reaction. Interestingly, the conjugated styrene **168** was not obtained in the reaction and we speculate that this is the result of electronic effect. It is expected, for example, that the "acidity" of the methylene protons adja-cent to the ring would be reduced if the carbazole is present as the conjugate anion (Figure 39).

Having established a route to the 8-allylcarbazole **134**, we then proceeded to continue with the remaining steps of our planned route. However, when the rearrangement

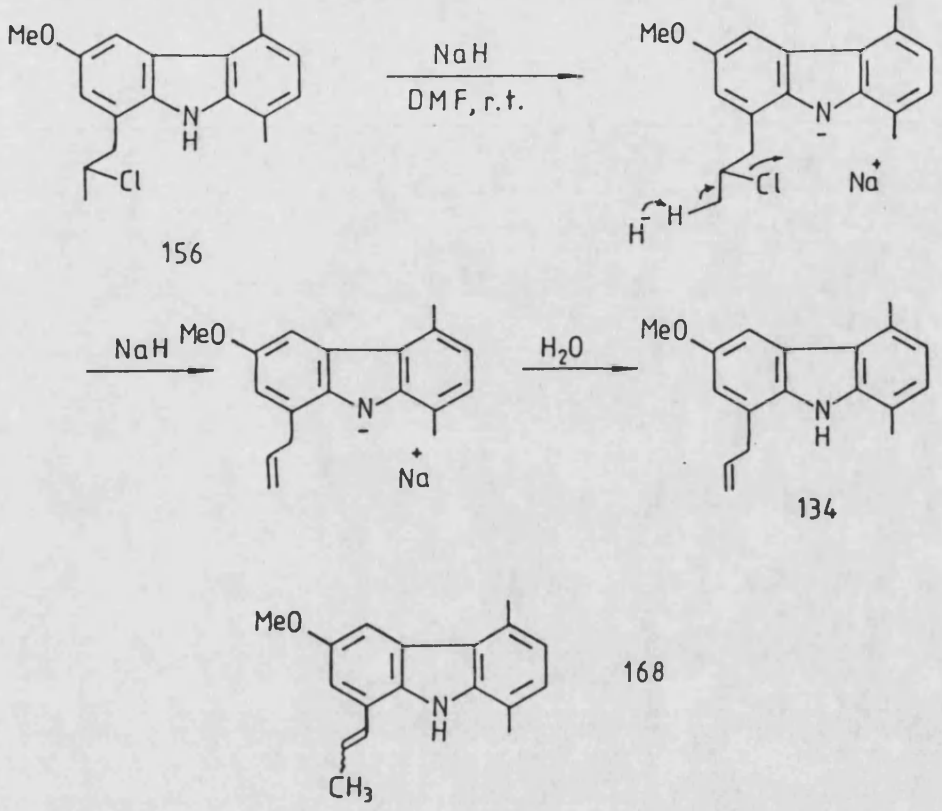
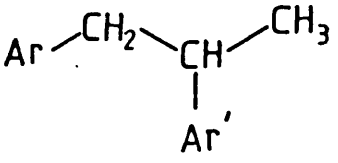


Figure 39

reaction was first scaled up, two new products **169** and **170** were isolated (Figure 40). For the mass spectrum of **169**, three major ion peaks at m/z 530, 292 and 238 are observed. We also noticed that the ^{1}H n.m.r. spectrum of this compound was very much like a composite of the relevant parts of the spectra of the monomeric allylcarbazoles **134** and **155**, particularly in the "aromatic" region. Indeed, the duplicated signals that are apparent in the spectrum for the resonances of the O-methyl, C-1 methyl and C-4 methyl protons gave a strong hint of a dimeric structure. Should

this be so then the lack of AB spin-spin system of the H-2 and H-3 proton resonances suggests that both carbazole monomers are either C-2 or C-3 substituted. The integral of the spectrum shows that only one allyl group is present, however two double doublets at 3.14 ppm and 3.02 ppm each due to a single proton resonance together with a single proton multiplet at 3.54 ppm signify that an addition of one carbazole nucleus has occurred to such a group to give a unit of the type:



Ar' ≡ carbazole nucleus

In support of this, a 3H doublet is observed at 1.29 ppm. This type of structure fits both the mass spectral data and an elemental analysis. From the aromatic proton resonances, it is clear that the ring A of one carbazole unit has an allyl group bonded to the C-8 (double doublets, J=2.4 Hz, at 7.62 ppm and 6.89 ppm). Whereas the other is unsubstituted (apart from the methoxyl group) for its signals form an AMX spin-spin system. Two further 1H singlets are observed at 7.27 ppm and 6.99 ppm and we assume that these represent the signals of the remaining aryl protons at C-2 in one monomer and C-2 in the other. Our presumption is governed by the fact that we consider the dimer results from the addition of the 3- and 8-allylated monomeric carbazoles. It would not make sense to postulate the formation of a 2-allylated intermediate.

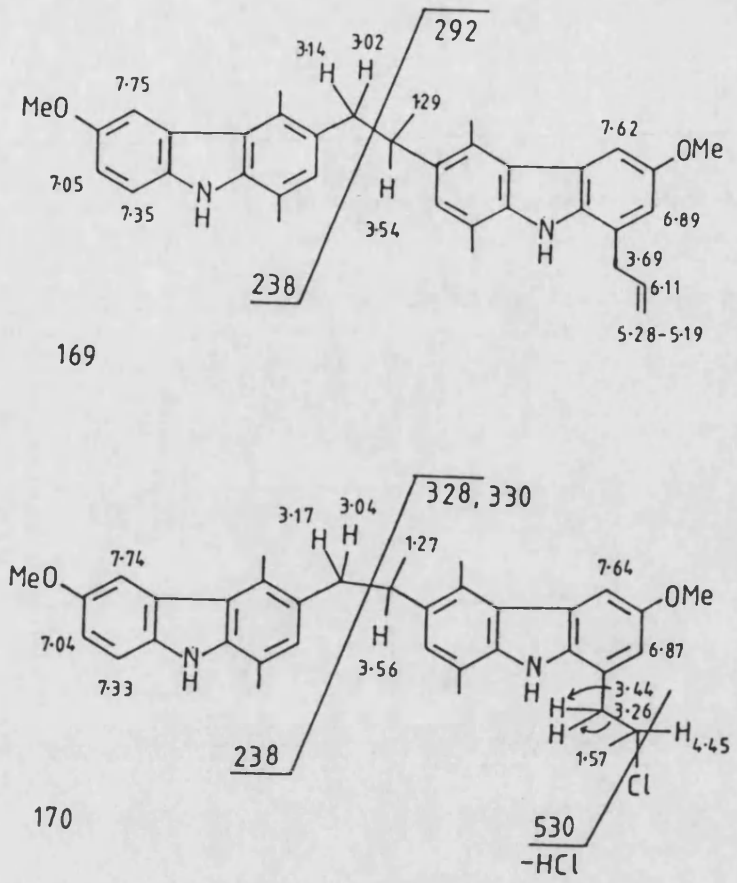


Figure 40

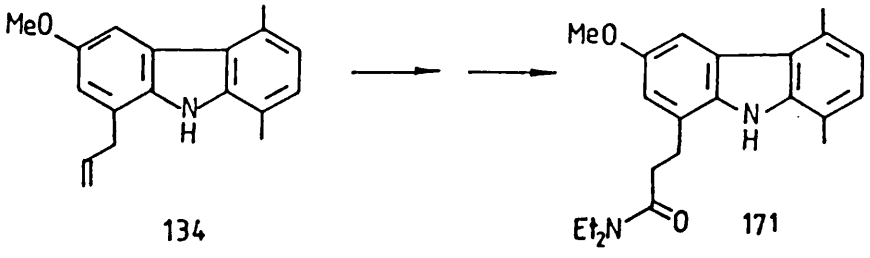
The structure of the other product **170** was similaly assessed. Its mass spectrum exhibits molecular ions at m/z 566 and 568, in the ratio of 3:1, typical of the isotopic abundance of one chlorine atom. The same duplicity was observed for a pair of peaks at m/z 328 and 330. Other major ion peaks at m/z 292 and m/z 238 were also present. The assignment of the ^1H n.m.r. spectrum of this product follows by comparison with those of the monomers **155** and **156** and a similarity to that of the first dimer. One feature of

the ^{1}H n.m.r. spectrum of this chloro compound is the duplication and hence broadening of signals and this may be attributed to the presence of the two possible pairs of diastereomers in the sample. In this respect, it is understandable that its melting point occurs over the range 189-195°C and is much lower than that of the parent structure **169** (241-243°C).

The formation of these two di-carbazolyl compounds is thought to be a result of over reaction. During the scaled-up operation, the reactant solution was more concentrated and the rise in reaction temperature caused by the complexation reaction between the N-allylcarbazole **132** and aluminum trichloride then promoted the rearrangement reaction and also a subsequent electrophilic substitution reaction between the C-3 and C-8 allylated carbazoles. This undesirable over reaction was easily avoided by carrying out the addition of the Lewis acid at a lower temperature (-30°C) and then allowing the reaction mixture to warm up gradually to room temperature.

3.2.3 Synthesis of the 7-substituted ellipticine **117**

The allyl group of the 8-allylcarbazole **134** was now to be transformed to the required side chain before D ring of the ellipticine tetracycle was constructed. This was conveniently achieved as described in the sequel.



134 171

The allylcarbazole 134 was first converted to the trans-styrene 168 by the catalytic action of bisacetonitrile palladium(II) chloride in benzene (Figure 41). Ozonolysis of the product at -20 °C provided the 8-formyl compound 172 in 79% yield after a reductive work-up using dimethyl sulphide. A Wittig-Horner reaction between this arylaldehyde 172 and the phosphonoacetamide 173 was then carried out. The phosphonate was prepared according to the procedure recommended by Landor et al. (146). Thus chloroacetyl chloride 175 was coverted to the amide 176 which then heated with triethyl phosphite to yield the required phosphonoacetamide 173. It was found that the Wittig-Horner reaction worked best when 2 mol equivalents of base (sodium hydride) were used; and then the desired unsaturated amide 174 was obtained as yellow crystalline solid in quantitative yield after stirring at room temperature for 24 h. The provision of an additional molar equivalent of base is necessary since the base also causes deprotonation of the carbazole. The unsaturated amide 174 was next reduced over palladium on activated carbon at 60 psi to afford the colourless product, amide 171.

Thus the stage was finally set for the D ring synthesis beginning with a formylation at the 3-position of the carbazole 171. Like other electrophilic substitution reactions of carbazoles, formylation largely takes place at the 3- and/or 6-positions which are the most electron rich sites next to the nitrogen atom (134). Dalton et al. (2) have prepared the 3-formylated product 178 from the carbazole 177 in 44% yield under Vilsmeier conditions (Figure 42).

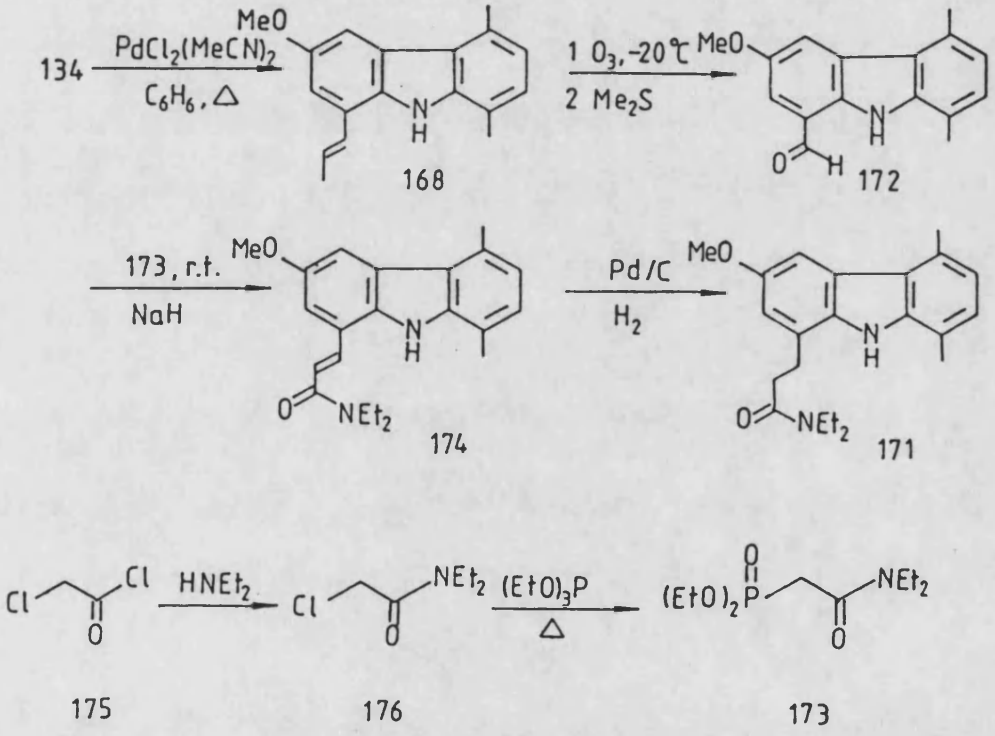
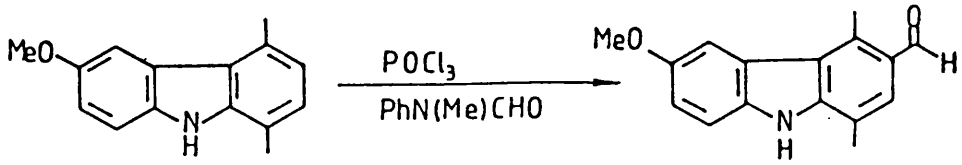


Figure 41



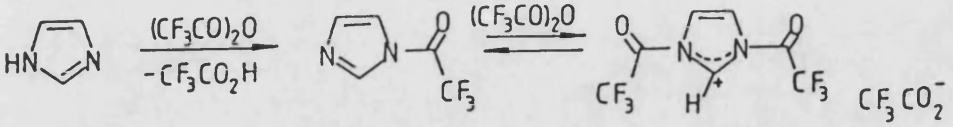
177 178

Figure 42

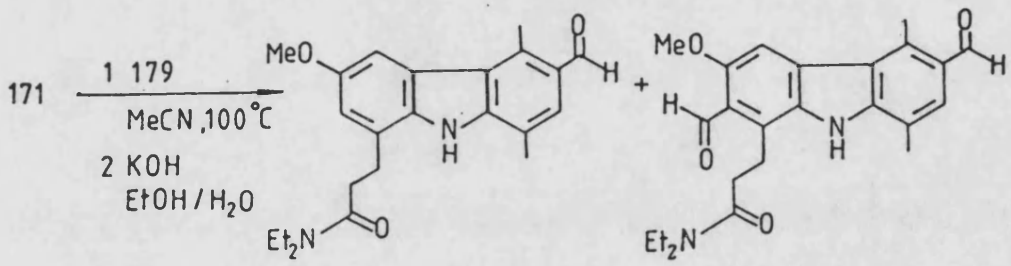
This reagent system is known to acylate ring A methoxylated carbazoles in this ring rather than in ring C so we chose to employ the more sterically demanding diacylimidazolium reagent **179** developed by Bergman et al. (147) (Figure 43). This furnished the desired product **180** after base hydrolysis of the intermediate N,N-diacylimidazolylcarbazole **182**. Unfortunately, this product was found to be contaminated with a diformylated compound **181**. The separation of these two compounds by chromatography was unsuccessful, nonetheless, the structure of this by-product was evident from the spectral data of the mixture.

In the mass spectrum, for example, it gives rise to a molecular ion peak at m/z 408, 28 units higher than that of the molecular ion of the mono-formylated compound. In the ^1H n.m.r. spectrum, two formyl protons resonate at 10.76 and 10.42 ppm, the original signal for H-7 in the spectrum of the starting material is no longer present, and the resonances of the first two pairs of methylene protons on the side chain at C-8 have also been affected by the

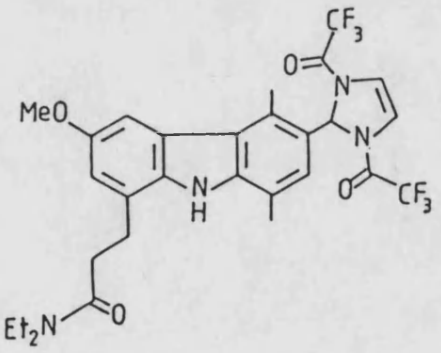
proximity of the carbonyl group. This causes down-field shifts of these signals from 3.37 to 3.68 ppm and from 2.77 to 2.92 ppm.



179



180 181



182

Figure 43

Rather than wasting time searching for conditions which would effect selective ring C formylation, we turned to the unsaturated compound **174** knowing that the conjugation between the alkenylamido side chain and the aromatic system would lower the electron density of the 7-position and hence deactivate it towards attack by the formylating agent **179**. In this way, the corresponding 3-formyl product **183** was obtained in good yield (83%) and diformylated products were not detected (Figure 44).

The double bond on the side chain was selectively reduced over palladium on activated carbon under mild conditions (Figure 44). But if excess time was given to the reaction, a new component began to form. This is believed to be the corresponding alcohol produced as a result of the reduction of the carbonyl group of the aldehyde **180**. The Schiff's base **184** was next prepared by heating the 3-formyl compound with excess 2-aminodimethoxyethane at 100°C. This product was sufficiently stable for handling although, in our work, we chose to reduce the crude product directly over Adams' catalyst to yield the amine **185**. This was then N-tosylated using tosyl chloride in pyridine to afford the sulphonamide **186** as colourless crystalline solid in 85% yield.

The conditions used in the formation of the D ring in this synthesis is analogous to the ring closure reactions employed by Jackson *et al.* (59) for the construction of isoquinolines. The limitation of the final cyclisation step

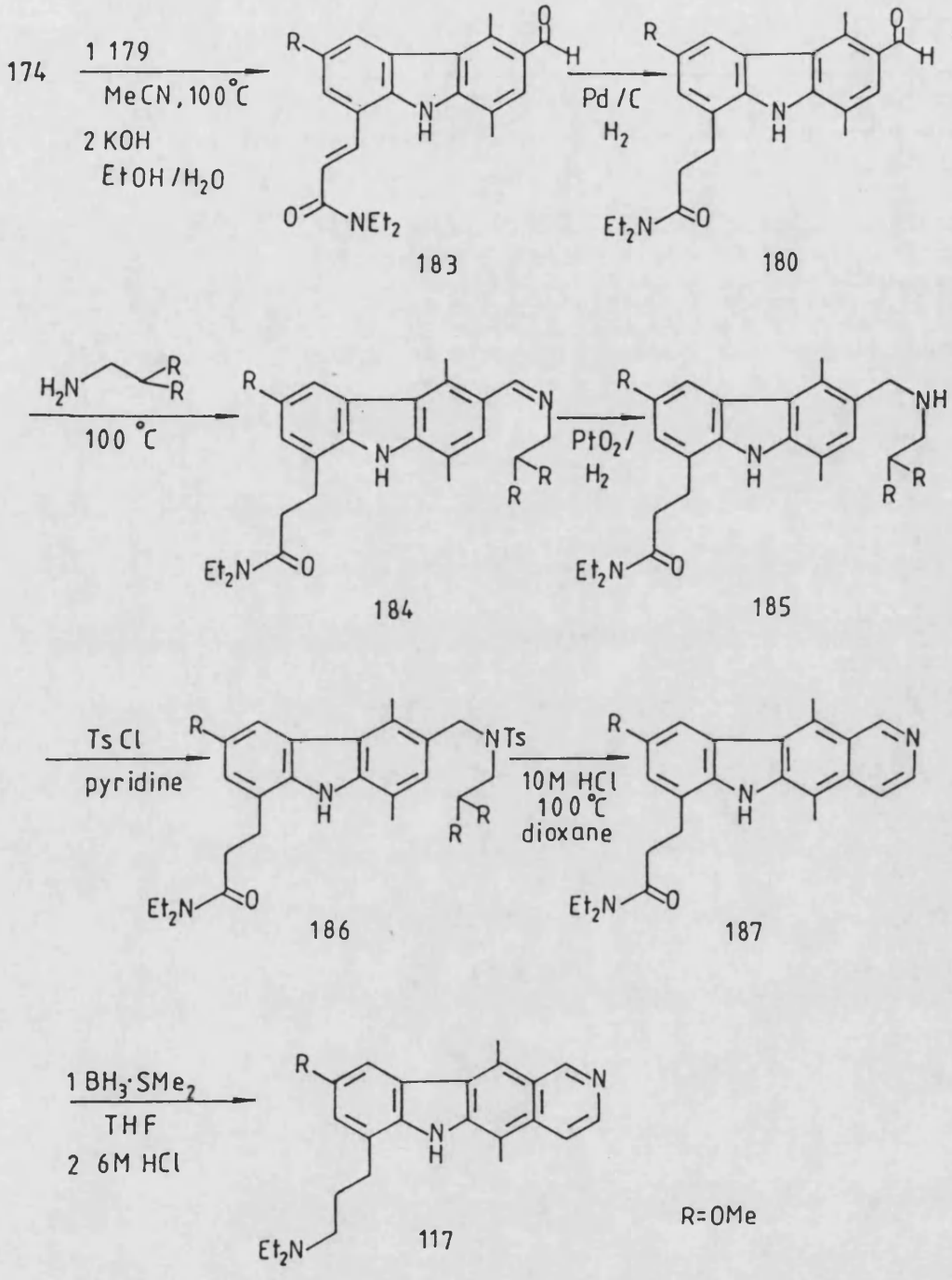
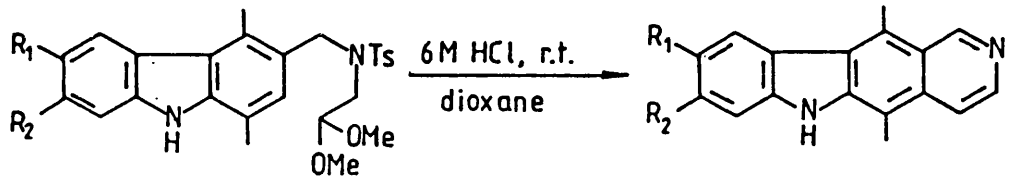

174
1 179
MeCN, 100°C
2 KOH
EtOH/H2O
183
Pd/C
H2
180
100 °C
184
PtO2/
H2
185
TsCl
pyridine
186
10M HCl
100°C
dioxane
187
1 BH3·SMe2
THF
2 6M HCl
117
R=OMe

Figure 44

is that it only works well on electron rich aromatic systems. Guthrie et al. (68) have employed this method in their synthesis of the ellipticines **96** and **97** (Figure 45). The usual cyclisation conditions are 6 M hydrochloric acid in dioxane at room temperature overnight.



$R_1R_2=CH_2OCH_2$ **96**

$R_1=R_2=OMe$ **97**

Figure 45

Following these recommendations, the sulphonamide **186** was treated with 6 M hydrochloric acid in dioxane at room temperature. After 55 h, all starting material had been consumed and the ellipticine **187** was obtained in about 30% yield. The reaction was sluggish and there was evidence that side-products were being formed. These impurities rendered purification quite tedious. In an effort to increase the rate of cyclisation and to minimise the possibility of acid hydrolysis of the amide, we decided to heat the reaction mixture and to use more concentrated acid. Accordingly, the reaction was repeated at 100 °C using 10 M hydrochloric acid in dioxane as reagent. As a result, the

reaction time was dramatically reduced to just over 3 h. The product was now easily isolated in 56% yield after column chromatography.

Reduction of amidoellipticine **187** to the amino-ellipticine **117** was effected by using borane-methyl sulphide complex (BMS) in tetrahydrofuran (Figure 44). This reagent is less sensitive towards oxygen and moisture than borane alone and is much more convenient to use (148). The role of this reagent in the reduction of amides to amines has been demonstrated by Brown *et al.* (149). Thus, following their literature conditions, the amide **187** in tetrahydrofuran under reflux and protected by an atmosphere of nitrogen, was treated with a 2M solution of the complex. The amide was completely reduced in 45 min and after acid hydrolysis of the resulting borane-amine complex, the final amine **117** was obtained in an unoptimized 51% yield.

The formylcarbazole **183** was also converted into the corresponding Schiff's base **188** but when it was hydrogenated over palladium on activated carbon, the expected amine **185** was not obtained. In contrast, sodium borohydride reduction of the imine in ethanol solution readily provided the amine **189** which was then tosylated as before, to afford **190** as a yellow solid (Figure 46). Attempts to ring-close this product to the ellipticine **191** failed and the tosylated compound **190** gradually decomposed in the presence of concentrated hydrochloric acid in dioxane. This failure is attributed to the deactivating

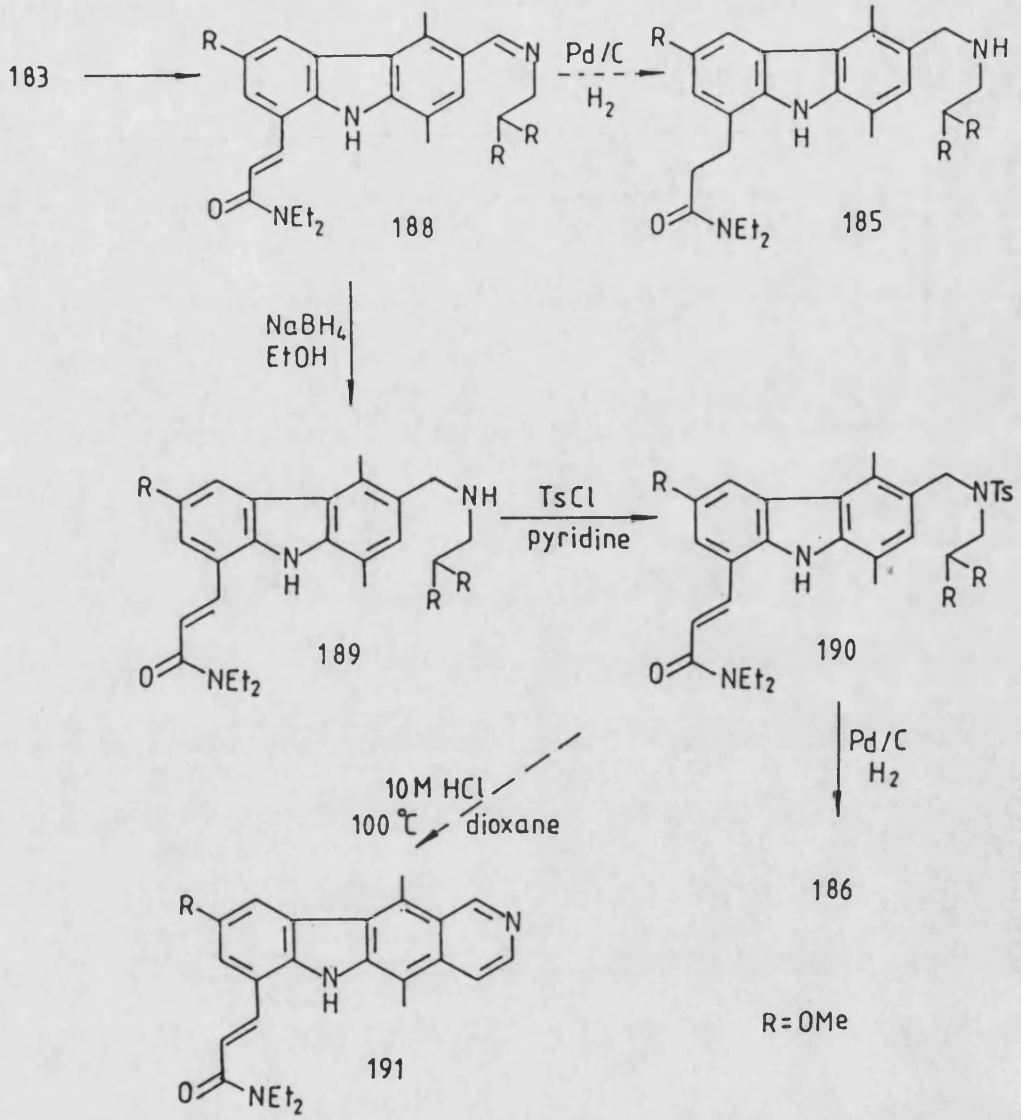


Figure 46

effect on the carbazole nucleus caused by conjugation between it and the unsaturated side chain. Indeed, no tetracyclic products were observed even after the amine was treated with acid at 100 °C for 24 h. Nevertheless, this carbazole **190** can be easily reduced over 10% w/w

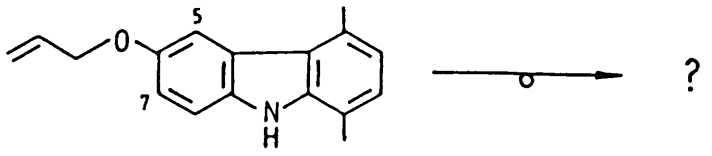
palladium on activated carbon to afford an alternative source of the useful intermediate **186** in quantitative yield.

3.3 Synthetic work towards 8-substituted ellipticine

3.3.1 Synthesis of C-5 and C-7 substituted carbazoles

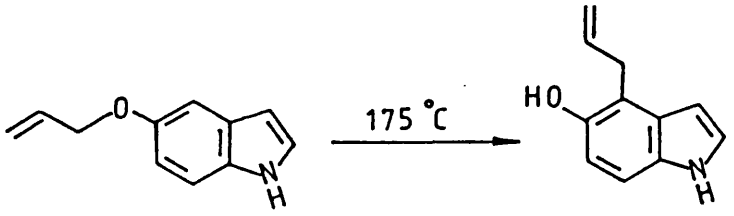
Parallel to our work on the aza-Cope rearrangement of N-allylcarbazoles, we have also investigated the rearrangement chemistry of the O-allylcarbazole **192**. The tactic was again to exploit the presence of a hetero-atom substituent as an internal "handle" for the introduction of another substituent onto the neighbouring position(s) which may otherwise be less readily accessible. Here we are interested in the C-7 allylated carbazole. The required material in this investigation was prepared from 3-methyl-4-nitrophenol. This was easily allylated by reaction with allyl bromide and sodium bicarbonate in acetone before being subjected to the same conditions employed previously in the synthesis of 5-methoxyindole (i.e. from **145** to **149** in Figure 32). The allyloxyindole **149** thus obtained was reacted with hexa-2,5-dione to furnish the desired carbazole **192**.

There is now an uncertainty over the regio-selectivity of the rearrangement process as both the 5- and 7-positions are available to accommodate the allyl group. A similar



192

situation had also been encountered by Julia et al. (150). In their synthesis of lysergic acid analogues, 4,5-di-substituted indoles were required. The 5-allyloxyindole **193** was thus prepared and subjected to a thermal Claisen rearrangement. The 4-allylindole **194** was obtained regio-specifically in 91% yield (Figure 47). The selectivity was apparently determined by the much higher electron density at the 4-position than at the 6-position of the indolic system.



193 194

Figure 47

In carbazole, this difference in electron density between the 5- and 7-positions also exists and there is a preference for bonding to the C-5. Indeed, after heating the allyloxycarbazole **192** for 60 h, under reflux in xylene,

only the 5-allyl isomer **195** was isolated in 80% yield (Figure 48). The possible steric interaction between the C-4 methyl group and the allyl group in the transition state does not seem to have any prohibitory effect on this pathway.

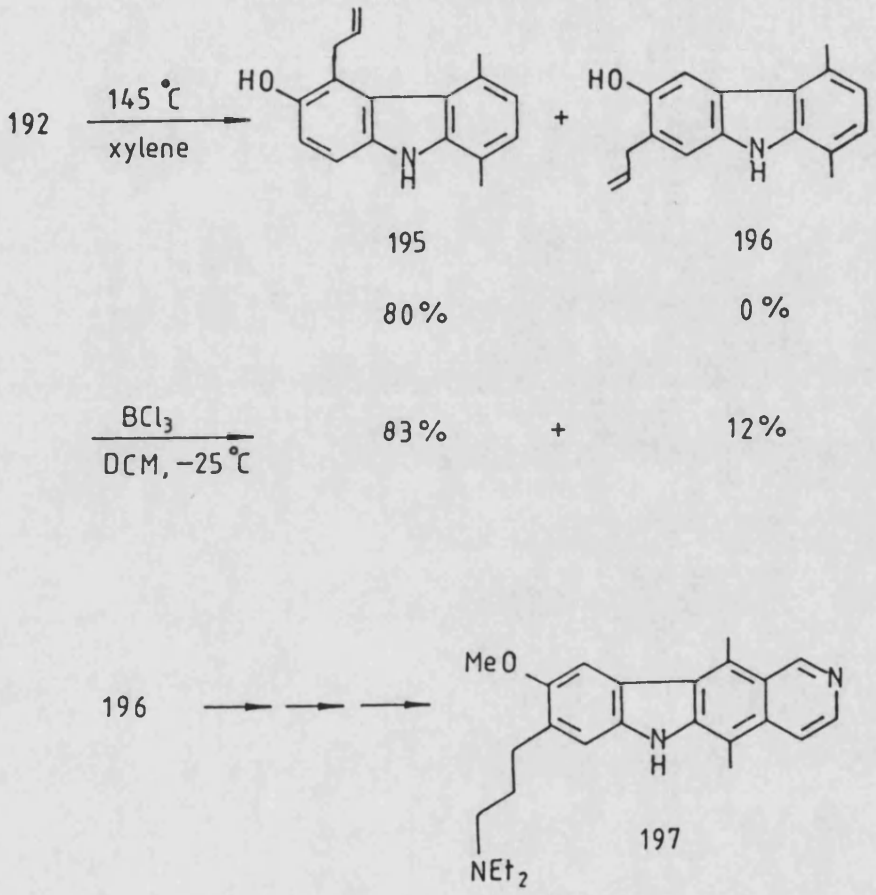


Figure 48

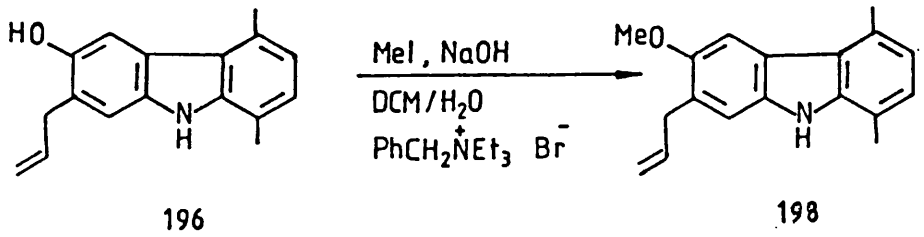
We next proceeded to investigate a charge-induced rearrangement reaction. Hence the allyloxycarbazole **192**

was treated with 1 mol equivalent of boron trichloride in dichloromethane at -25 °C. The reaction was complete in 30 min and two products were isolated in 83% and 12% yield. The major product was shown to be identical with the 5-allylcarbazole **195**, obtained previously. Thus its aryl substitution pattern was readily determined from the ^{1}H n.m.r. spectrum in which there are four doublets representing the signals of the four aromatic C-H protons, two of which are at 7.02 and 6.81 ppm, and are assigned to be the ortho-coupled H-2 and H-3 protons. The other two doublets at 7.29 and 7.05 ppm, share a coupling constant of J=8.4 Hz and are assigned as the ortho-coupled H-7 and H-8 resonances.

The assignment of the ^{1}H n.m.r. spectrum for the minor isomer **196** was also straightforward; there are for example, two doublets, sharing a coupling constant of J=7.3 Hz, at 7.08 and 6.87 ppm. These arise from the resonances of the H-2 and H-3 protons respectively. There are also two singlets at 7.61 and 7.20 ppm; the downfield signal is associated with the resonance of H-5 and the other with that of H-8. The interesting outcome of this reaction is that the presence of boron trichloride has greatly reduced the reaction time and temperature and increased the yield. The most significant fact is however that it has also affected the regio-specificity of the reaction. Although the 7-substituted isomer obtained could be used as a suitable starting material for preparing the 8-substituted

ellipticine **197**, we have yet to find ways of controlling the amount of undesired 5-allylated product

O-Methylation (151) of the carbazole **196** to give **198** was achieved using methyl iodide and sodium hydroxide in a mixed dichloromethane/water system with benzyl triethylammonium chloride as the phase transfer agent (Figure 49). The alternative N-methylated product was not obtained from this reaction, however; the N-alkylation of certain carbazoles under similar conditions has been reported previously (152).



196 198

Figure 49

3.3.2 Synthesis of the amidopropylindole **208**

Another attempt to prepare the 8-substituted ellipticine **197** was also carried out. Here, the key intermediate was to be the functionalised carbazole, **200**. For this the precursor should be the indole **199** and we anticipated to obtain this compound by the cyclisation of a suitable aniline **201** (Figure 50).

The formation of indoles from the corresponding anilinoacetaldehyde acetals *via* an intramolecular ring closure is attractive and such reactions have been studied in recent years (153-154). This route is particularly useful for preparing 2,3,7-unsubstituted indoles bearing electron donating groups in the aromatic ring. A potential synthesis was accordingly drawn up (Figure 51).

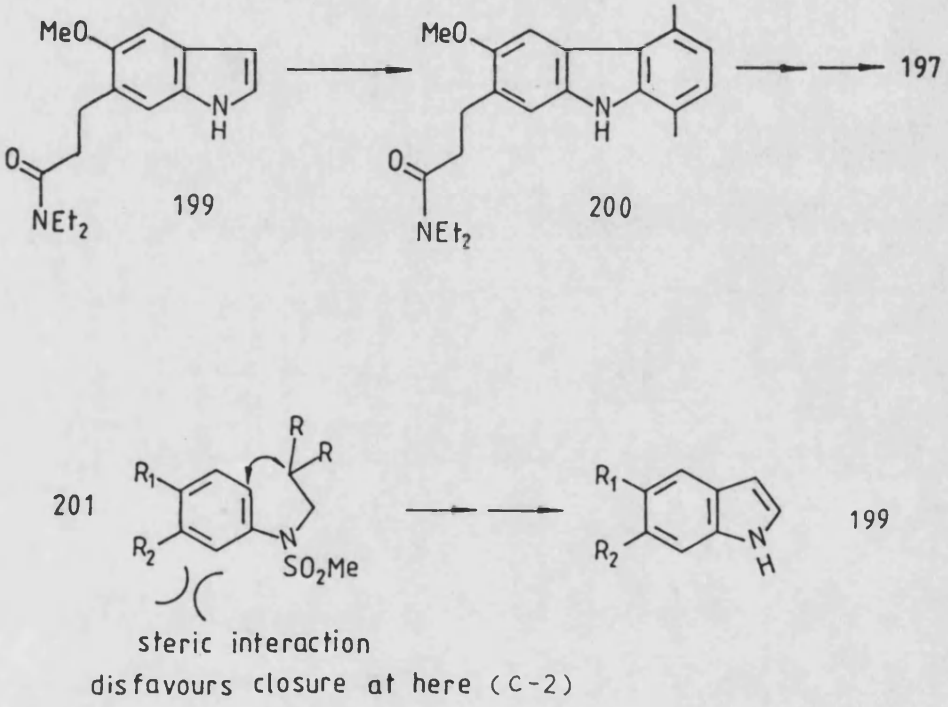


Figure 50

Although, in theory, cyclisation can take place at the two available *ortho*-positions in the aniline **201**, it is expected that one of them is not easily accessible due to

the presence of the sterically demanding side chain at its neighbouring position. In practice, the benzaldehyde **202** was efficiently converted to the cinnamic acid **203** by reaction with malonic acid in pyridine and piperidine (155). At this stage, the acid **203** can either be reduced to give the amino propionic acid **204** or converted into the amide **205**. It was noticed that the amine **204** actually exists in its zwitterionic form as evidenced by its exceptionally high melting point (decomp. 276 °C) and its spectroscopic data. Thus the IR spectrum exhibits a broad band at 2800-2400 cm^{-1} indicating quaternary N-H streching. The ^{1}H n.m.r. spectrum shows no carboxylic acid proton resonance, but a broad peak is present at 6.5-5.1 ppm, ranging across 50 Hz and integrating to three protons (which are exchangeable with the deterions of deuterated water).

The amide **205** was formed by treatment of the acid first with thionyl chloride, and then with diethylamine. Reduction of this amide over palladium on activated carbon furnished the substituted aniline **206** in good yield. This product was N-sulphonylated using methylsulphonyl chloride in pyridine as reagent and the anilide **207** was formed in 82% yield. Alkylation of the latter by 2-bromodiethoxyethane and sodium hydride provided the anilinoacetal **201** as a colourless oil (76%). In the literature examples, the last ring closure reaction is normally achieved by the action of a Lewis acid such as titanium tetrachloride (154). We therefore treated the acetal **201** with titanium tetra-

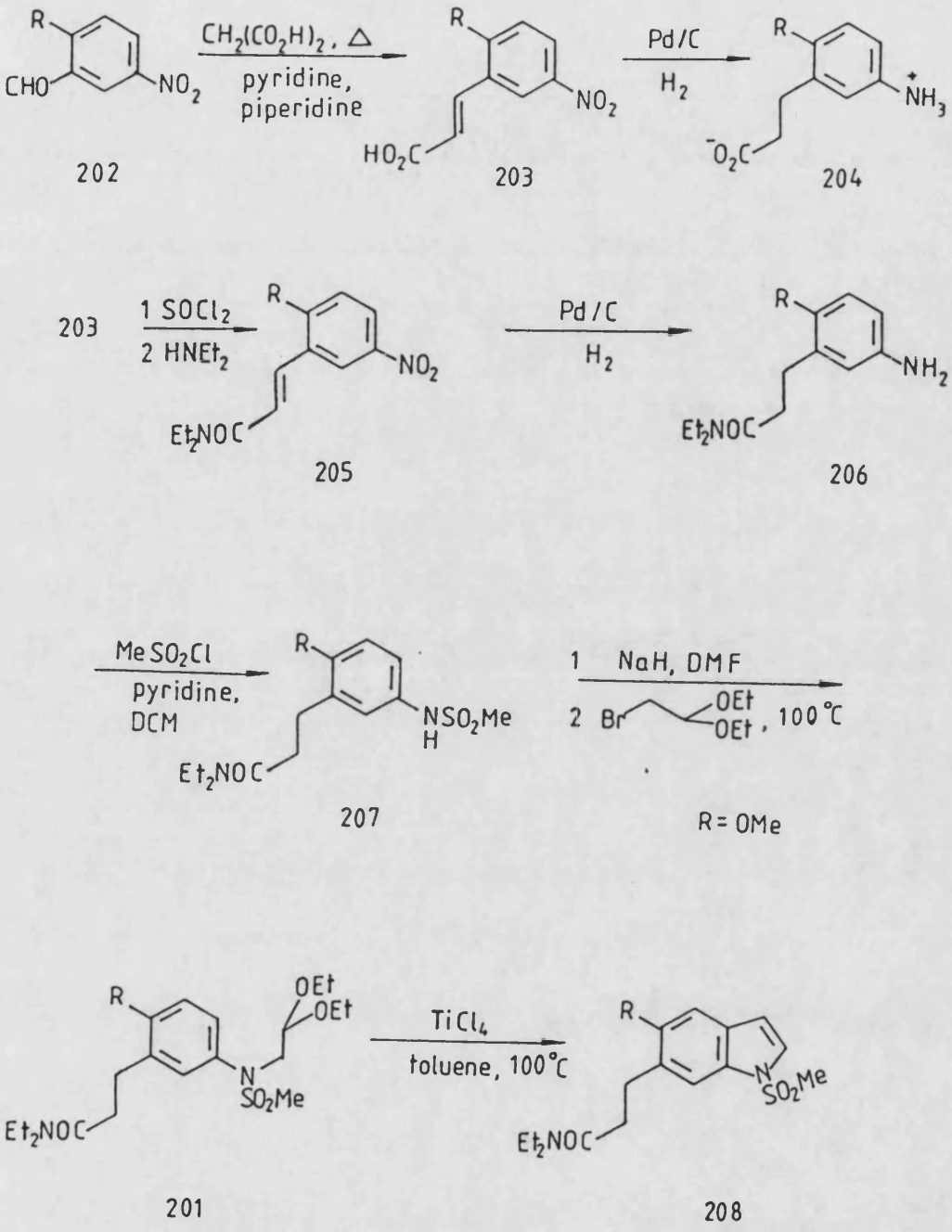

R
CHO
NO2
CH2(CO2H)2, Δ
pyridine,
piperidine
HO2C
Pd/C
H2
NH3
O2C
202
203
204
1 SOCl2
2 HNEt2
Et2NOC
205
206
MeSO2Cl
pyridine,
DCM
NSO2Me
H
1 NaH, DMF
2 Br
OEt
OEt
, 100°C
R = OMe
TiCl4
toluene, 100°C
SO2Me
201
208

Figure 51

chloride in dry toluene at room temperature. After stirring under nitrogen for several hours, tlc analysis of the reaction mixture indicated all starting material has been consumed and a multi-component product mixture was obtained. The ^{1}H n.m.r. spectrum of this crude mixture exhibits a resonance at 10.2 ppm indicating the presence of an aldehyde. This result points to the fact that the ring closure step had not occured and formation of an aldehyde could be a result of deprotection of the acetal function. The reaction was therefore repeated at higher temperature in the hope of achieving cyclisation. However, a best yield of 9% for the required indole **208** was only obtained as the only product when the reaction mixture was heated to 110 °C for 20 min. Under these conditions the majority of starting material seemed to have polymerised to give a dark tarry residue. At this stage, it was decided that this work should be postponed so that we could concentrate our efforts on the other more promising route to 7-substituted ellipticines, the results of which have already been described.

Section IV

Experimental

General

Chemicals, solvents and reagents were purified and dried, where appropriate, before use by standard methods. Preparative column chromatography was normally carried out on silica gel 60 GF7736 (E. Merck) or on alumina (Camag) (Fisons 100-250 mesh). Thin-layer chromatography (tlc) was carried out routinely on silica gel 60 GF254 (E. Merck). Proton (^{1}H n.m.r.) and Carbon-13 (^{13}C n.m.r.) nuclear magnetic resonance spectra were recorded for deuterated chloroform solutions, unless stated otherwise, on a JEOL GX270 instrument. Chemical shifts are expressed in ppm downfield from tetramethylsilane (TMS) as standard and coupling constants (J) in Hz. Ultra-violet/visible spectra (UV) were recorded for 95% ethanolic solutions on a Perkin-Elmer Lambda-3 spectrophotometer. Infra-red (IR) spectra were measured as Nujol mulls (N), chloroform solutions (S) or liquid films (L), on a Perkin-Elmer 1310 instrument. Mass spectra (MS) were recorded on an A.E.I. MS12 mass spectrometer at 70 eV. Mass to charge ratios are quoted and their relative intensity (%) are enclosed in parentheses.

Normally, where solvents had to be removed, a rotary evaporator operating at water-pump pressure was employed: exceptions to this routine are noted. Petroleum ether (60-80°) was used.

Diethyl 3-(2-aminophenyl)propionamide **128**. — A solution of o-nitrocinnamic acid (19.3 g, 100 mmol) in thionyl chloride (100 cm^3) was heated under reflux for 2.5 h. Excess thionyl chloride was removed. The residue was dissolved in dry benzene (150 cm^3) and efficiently stirred at 0 °C. To this solution, was added dropwise diethylamine (17.5 g, 250 mmol). The resultant mixture was stirred at 0 °C for 30 min and at 70 °C for 3 h. The solvent was then removed at ambient temperature. The residue was taken up in ethyl acetate (250 cm^3) and the solution was washed with water (2x 100 cm^3), and then with saturated brine (100 cm^3). The dried ($MgSO_4$) organic layer was then hydrogenated in the presence of palladium (10% on activated carbon) (0.2 g), at 100 psi. The hydrogenation mixture was filtered through a bed of celite to remove the catalyst and the filtrate was evaporated to dryness. Crystallisation of the product from petroleum ether gave the title compound as a colourless solid (20.2 g, 92%), m.p. 69 °C, IR(N) 3400, 3340, 3250 and 1600, ^1H n.m.r.(100 MHz) 7.12-6.92 and 6.80-6.20 (4H,m, Ar-Hs), 4.07 (2H,br s,NH_2), 3.47-3.08 (4H,2q,J=7.1 Hz, $N(C\underline{H}_2CH_3)_2$), 3.00-2.29 (4H,m,$C\underline{H}_2C\underline{H}_2CONEt_2$), 1.17-0.96 (6H, 2t,J=7.1 Hz,$N(CH_2C\underline{H}_3)_2$), Acc. MS(m/z) 220.158($M^+$, 81.2%; calc. 220.158), 148.075(62.1%), 147.067(41.7%), 119.074 (67.3%).

Attempted preparation of hydrazine **118** :

(I) using tin(II) chloride as the reducing agent. — To

concentrated hydrochloric acid (6 M, 15 cm^3), powdered amidopropylaniline 128 (2.2 g, 10 mmol) was added in portions. The resultant solution was stirred at 0 °C as a solution of sodium nitrite (0.8 g, 11 mmol) in water (3 cm^3) was added dropwise. The mixture was stirred at 0 °C for 10 min. A solution of tin(II) chloride (2.28 g, 12 mmol) in concentrated hydrochloric acid (6 M, 0.5 cm^3) was gradually introduced causing the formation of a heavy yellow paste. After stirring at room temperature for 30 min, the mixture was filtered under suction and the solid which was collected then stirred in a mixture of aqueous sodium hydroxide (40%, 50 cm^3) and ether (50 cm^3) at 0 °C. The aqueous layer was separated and extracted with more ether (2x 25 cm^3), these combined extracts and the ether layer were concentrated to about 20 cm^3. Hydrogen chloride gas was bubbled through the cooled ether solution, which was later diluted with more ether (50 cm^3), washed with saturated sodium hydrogen carbonate solution (30 cm^3), water (2x 30 cm^3) and saturated brine (30 cm^3). The dried ($MgSO_4$) organic layer was evaporated to afford a red viscous oil which could not be characterised.

(II) using sodium sulphite as the reducing agent. — To the diazotised solution prepared as described in (I), at 0 °C, was added dropwise a cold solution of sodium sulphite (2.66 g, 21 mmol) in water (6 cm^3). The mixture was then stirred at room temperature for 60 min and at 60 °C for 30 min. It was again cooled to 0 °C. The solid precipitate

was filtered and recrystallised from ethanol to yield a colourless solid which proved to be diethyl 3-(2-hydroxyphenyl)propionamide **130** (0.47 g, 21%), m.p. 127°C, IR(N) 3160, 1600, 1590 and 1260, MS(m/z) 221(M^+, 80%), 204(20%), 149(26%) and 120(40%).

Tripiperidinomethane. — Piperidine (153.3 g, 1.8 mol), triethyl orthoformate (133.4 g, 0.9 mol) and acetic acid (3.6 g, 0.06 mol) were combined in a three-necked round bottom flask equipped with a thermometer and a steam-jacketed condenser. The reactants were gently heated to reflux (initial boiling point of the mixture was ca. 110°C) for 12 h. The by-product, ethanol was allowed to evaporate through the steam-jacketed condenser during the reaction. After the boiling point of the reaction mixture had risen above 145°C (12 h), the heat was discontinued and the mixture was allowed to cool to room temperature overnight. Lower boiling by-products were removed on a rotary evaporator and vacuum distillation of the concentrate firstly afforded N-formylpiperidine (20.1 g), b.p. 55-60°C/0.2 mm Hg, which was followed by a fraction consisting of the colourless title compound (67.1 g, 42%), b.p. 135-145°C/0.2 mm Hg (lit.,[156] 98-106°C/0.05-0.1 mm Hg), ^{1}H n.m.r.(60 MHz) 3.12 (1H,s,C<u>H</u>), 2.57 (12H,m,3x(C<u>H</u>$_2$NC<u>H</u>$_2$)), 1.42 (18H,m,3x -(C<u>H</u>$_2$)$_3$-).

3-Methyl-4-nitro(prop-2-enyloxy)benzene **145**. — A

mixture of 3-methyl-4-nitrophenol (61.2 g, 400 mmol), anhydrous potassium carbonate (66.2 g, 480 mmol) and distilled allyl bromide (58.0 g, 480 mmol) in acetone (800 cm^3) was heated under reflux for 6 h. The reaction mixture was cooled to room temperature and the inorganic precipitate was filtered off, then the filtrate was evaporated to dryness. The residue was taken up in ethyl acetate (300 cm^3) and washed with water (2x 150 cm^3), saturated brine (150 cm^3), dried ($MgSO_4$) and the solvent removed. Crystallisation of the residue from petroleum ether afforded the title compound as a colourless solid (71.8 g, 93%), m.p. 34°C, IR(N) 1600, 1580, 1320, 1250, ^1H n.m.r. 8.09 (1H,m,H-5), 6.81 (2H,m,H-2 and H-6), 6.04 (1H,m, $C\underline{H}=CH_2$), 5.40 (2H,m,CH=$C\underline{H}_2$), 4.61 (2H,m,OCH_2), 2.62 (3H,s,CH_3), MS(m/z) 193(M^+), 176, 41(100%).

5-(Prop-2-enyloxy)indole **149**. — A mixture of nitrotoluene **145** (5.0 g, 26 mmol) and tripiperidinomethane (10.3 g, 39 mmol) was heated at 110°C for 9 h, under reduced pressure (15 mmHg). The red viscous oil which remained was dissolved in a minimum amount of acetone, and transferred to a separating funnel charged with a buffered mixture of titanium(III) chloride solution (100 cm^3, 20% w/v solution in diluted hydrochloric acid) and ammonium acetate (4 M, 300 cm^3). The contents of the separating funnel were shaken for 10 min before being extracted exhaustively with ether. The combined ether layers were washed with saturated sodium

hydrogen carbonate solution, water, saturated brine, dried ($MgSO_4$) and the solvent removed to give an oily residue. Column chromatography on silica gel, eluting with ethyl acetate in petroleum ether, afforded the title compound as an amber oil (2.7 g, 61%), IR(L) 3400, 3090, 1610, 1210, ^{1}H n.m.r. 7.95 (1H,br s,NH), 7.15 (1H,d,J=8.8 Hz,H-7), 7.11 (1H,d,J=2.4 Hz,H-4), 7.03 (1H,m,H-2), 6.87 (1H,dd,J=2.4, 8.8 Hz,H-6), 6.43 (1H,m,H-3), 6.08 (1H,m,C<u>H</u>=CH_2), 5.41 (1H,m,CH=C<u>H</u>(H)), 5.25 (1H,m,CH=CH(<u>H</u>)), 4.54 (2H,m,OCH_2), ^{13}C n.m.r. 152.9, 133.8, 131.0, 128.1, 124.95, 117.4, 112.8, 111.7, 103.7, 102.15, 69.7, MS(<u>m/z</u>) 173(M^+, 45%), 132(100%), 104(55%).

A minor by-product, a brown oil (22 mg) was also isolated. This was shown to be 2,2-<u>bis</u>[3-(5-<u>propenyloxy</u>)<u>indolyl</u>]<u>propane</u> **153**, IR(L) 3400, 2900, 1600, ^{1}H n.m.r. 7.77 (2H,br s,2xNH), 7.14 (2H,d,J=8.8 Hz,2xH-7), 7.00 (2H,d,J=2.4 Hz,2xH-2), 6.84 (2H,d,J=2.4 Hz,2xH-4), 6.75 (2H,dd,J=8.8,2.4 Hz,2xH-6), 5.95 (2H,m,2x(C<u>H</u>=CH_2)), 5.28 (2H,m,2x(CH=C(<u>H</u>)H)), 5.16 (2H,m,2x(CH=C(H)<u>H</u>)), 4.33 (4H,m,2x(OCH_2)), 1.85 (6H,s,2x(CH_3)), ^{13}C n.m.r. 151.8 (C-5), 133.9 (<u>C</u>H=CH_2), 132.5 (C-7a), 126.6 (C-3a), 124.9 (C-3), 121.3 (C-2), 117.4 (CH=<u>C</u>H_2), 111.8, 111.5, 105.2 (C-4,C-5,C-6), 69.8 (OCH_2), 34.6 (CMe_2), 29.7 (CH_3), MS(<u>m/z</u>) 386(M^+), 173(100%), 172 [Found: C, 77.5; H, 7.1; N, 7.05. $C_{25}H_{26}N_2O_2$ requires: C, 77.7; H, 6.8; N, 7.25%].

5-<u>Methoxyindole</u> **137**. — The same procedure as

described in the previous experiment was used with 3-methyl-4-nitromethoxybenzene (5.0 g, 30 mmol). The title compound was thus obtained as a colourless solid (2.43 g, 55%), m.p. 58 °C (lit.[157] 59 °C), IR(N) 3400, 1620, ^{1}H n.m.r. 8.05 (1H,br s,NH), 7.39-7.12 (3H,m,H-2,H-4 and H-7), 6.91 (1H,dd,J=8.8, 3.0 Hz,H-6), 6.55 (1H,m,H-3), 3.85 (3H,s, OCH_3), MS(m/z) 147(M^+, 100%), 132.

1,4-Dimethylcarbazole **24**. — To a stirred solution of 4-toluenesulphonic acid monohydrate (9.5 g, 50 mmol) in absolute ethanol (50 cm^3) heated under reflux in a dry atmosphere, was added indole (11.7 g, 100 mmol) and hexa-2,5-dione (11.4 g, 140 mmol) in absolute ethanol (200 cm^3) over a period of 90 min. The resultant mixture was heated under reflux for another 4 h and then allowed to cool. The solvent was removed to yield a dark red residue. Column chromatography on silica gel, eluting with dichloromethane (30%) in petroleum ether, gave the title compound as a colourless solid (11.8 g, 61%), m.p. 93-94 °C (lit.[58] 96 °C), ^{1}H n.m.r. 8.15 (1H,dd,J=7.9, 1.0 Hz,H-5), 7.86 (1H,br s,NH), 7.40 (1H,d,J=1.0 Hz,H-8), 7.38 (1H,m,H-7), 7.23 (1H,m,H-6), 7.10 (1H,d,J=7.3 Hz,H-2), 6.91 (1H,d,J=7.3 Hz,H-3), 2.82 (3H,s,4-CH_3), 2.46 (3H,s,1-CH_3).

1,4-Dimethyl-6-methoxycarbazole **138**. — The same procedure as described in the previous experiment was used with 5-methoxyindole (14.7 g, 100 mmol) as the starting

material. The title compound was obtained as a colourless solid (17.9 g, 80%), m.p. 132-133 °C (lit.[7] 136.5 °C), UV 222, 275, IR(N) 3400, 1510, 1580, 1200, 800, ^{1}H n.m.r. 7.86 (1H,br s,NH), 7.68 (1H,d,J=2.5 Hz,H-5), 7.36 (1H,d,J=8.7 Hz, H-8), 7.10 (1H,d,J=7.1 Hz,H-2), 7.06 (1H,dd,J=8.7, 2.5 Hz, H-7), 6.89 (1H,d,J=7.1 Hz,H-3), 3.93 (3H,s,OCH_3), 2.83 (3H,s,4-CH_3), 2.50 (3H,s,1-CH_3), ^{13}C n.m.r. C 153.7, 139.7, 134.4, 130.8, 125.0, 121.4, 117.1, CH 126.1, 120.5, 113.5, 110.9, 106.4, CH_3 56.2, 20.5, 16.6, MS(m/z) 225(M^+, 100%), 210(92%).

1,4-Dimethyl-6-(prop-2-enyloxy)carbazole **192**. — The same procedure as described in the previous experiment was repeated now with 5-propenyloxyindole **149** (17.3 g, 100 mmol) and the title compound was obtained as a colourless solid (20.3 g, 81%), m.p. 140-141 °C, UV 230, 244, 255(sh), 265, 295, IR(N) 3440, 1630, 1600, 1240, 1215, 820, ^{1}H n.m.r. 7.80 (1H,br s,NH), 7.70 (1H,d,J=2.4 Hz,H-5), 7.32 (1H,d,J=8.6 Hz,H-8), 7.09 (1H,d,J=7.1 Hz,H-2), 7.06 (1H,dd, J=8.6, 2.4 Hz,H-7), 6.88 (1H,d,J=7.1 Hz,H-3), 6.14 (1H,m, C<u>H</u>=CH_2), 5.47 (1H,m,CH=C(<u>H</u>)H), 5.30 (1H,m,CH=C(H)<u>H</u>), 4.64 (2H,m,OCH_2), 2.81 (3H,s,4-CH_3), 2.47 (3H,s,1-CH_3), MS(m/z) 251(M^+, 38%), 210(100%) [Found: C, 81.1; H, 7.0; N, 5.5. $C_{17}H_{17}NO$ requires: C, 81.2; H, 6.8; N, 5.6%]

1,4-Dimethyl-9-(prop-2-enyl)carbazole **131**. — To a stirred suspension of sodium hydride (2.4 g of 60% in oil

dispersion, 60 mmol) in dry dimethylformamide (90 cm^3) at 0 °C under nitrogen, was added the carbazole 24 (9.75 g, 50 mmol) in dry dimethylformamide (50 cm^3). After the addition, the mixture was stirred for a further 10 min and freshly distilled allyl bromide (7.25 g, 60 mmol) in dry dimethylformamide (10 cm^3) was then slowly introduced. The resultant solution was stirred at room temperature for 15 min and then maintained at 50 °C for 6 h. After this time, the reaction mixture was cooled to room temperature and poured into cold, stirred water (300 cm^3) and extracted with ethyl acetate (3x 200 cm^3). The combined organic layers were washed with water (3x 150 cm^3), saturated brine (100 cm^3), dried ($MgSO_4$) and the solvent removed. Column chromatography of the residue on silica gel, eluting with dichloromethane (20%) in petroleum ether, afforded the product as colourless prisms (10.6 g, 90%), m.p. 106 °C, IR(N) 3080, 3050, 3020, 1640, 1600, 900, ^1H n.m.r. 8.16 (1H,m,H-5), 7.39 (1H,m,H-7), 7.29 (1H,d,J=7.4 Hz,H-8), 7.21 (1H,m,H-6), 7.05(1H,d,J=7.3 Hz,H-2), 6.86 (1H,d,J=7.3 Hz,H-3), 6.07 (1H,m,C<u>H</u>=CH_2), 5.12 (2H,m,CH=C<u>H</u>$_2$), 4.83 (2H,m,NCH_2), 2.84 (3H,s,4-CH_3), 2.74 (3H,s,1-CH_3), ^{13}C n.m.r. 142.0, 139.5, 133.8, 130.9, 128.6, 124.8, 123.7, 122.4, 122.0, 120.8, 119.0, 117.1, 116.0, 108.4, 46.7, 20.8, 19.5, Acc. MS(<u>m/z</u>) 235.136(M^+, 100%; calc. 235.136), 208.112(13%), 194.095(95%).

6-<u>Methoxy</u>-1,4-<u>dimethyl</u>-9-(<u>prop</u>-2-<u>enyl</u>)<u>carbazole</u>

132. — The same procedure as described in the previous

experiment was used again with methoxycarbazole 137 (11.25 g, 50 mmol) as starting material. The title compound was thus obtained as colourless needles (12.2 g, 92%), m.p. 139 °C, UV 232, 245(sh), 268, 295, IR(N) 1610, 1570, 1480, 1200, 1140, 910, ^{1}H n.m.r. 7.71 (1H,d,J=2.6 Hz,H-5), 7.24 (1H,d,J=8.8 Hz,H-8), 7.08 (1H,dd,J=8.8, 2.6 Hz,H-7), 7.05 (1H,d,J=7.4 Hz,H-2), 6.86 (1H,d,J=7.4 Hz,H-3), 6.05 (1H,m,C<u>H</u>=CH_2), 5.12 (2H,m,CH=C<u>H</u>$_2$), 4.82 (2H,m,NCH_2), 3.93 (3H,s,OCH_3), 2.84 (3H,s,4-CH_3), 2.73 (3H,s,1-CH_3), ^{13}C n.m.r. 155.1, 141.4, 137.9, 135.7, 132.8, 130.3, 125.7, 123.5, 122.0,119.2, 117.5, 114.9, 110.7, 108.1, 57.8, 48.6, 22.5, 21.2, MS(<u>m/z</u>) 265(M^{+}, 27%), 255(50%), 254(40%), 224(33%), 213(80%), 212(60%), 41(100%) [Found: C, 81.4; H, 7.5; N, 5.2. $C_{18}H_{19}NO$ requires: C, 81.5; H, 7.2; N, 5.3%].

<u>Rearrangement of 1,4-dimethyl-9-(prop-2-enyl)carbazole 131 with aluminum trichloride in dichloromethane</u>. — To an efficiently stirred solution of the carbazole 131 (235 mg, 1 mmol) in dry dichloromethane (50 cm^3) at 20 °C, a suspension of freshly ground aluminum trichloride (160 mg, 1.2 mmol) in dry dichloromethane (2 cm^3) was added in small portions. The mixture was stirred at room temperature for 9 h under nitrogen. It was then poured into cold water (50 cm^3) and the aqueous layer was extracted with dichloromethane (2x 30 cm^3). The combined organic layers were washed with water (2x 30 cm^3), saturated brine (40 cm^3), dried ($MgSO_4$) and the solvent removed to give a

solid residue. Column chromatography on silica gel, eluting with dichloromethane (30%) in petroleum ether, afforded two isomeric products, A and B in that order:

Product A, 1,4-dimethyl-6-(prop-2-enyl)carbazole **140** (108 mg, 46%), m.p. 76-77 °C, UV 223(sh), 242, 250(sh), 259, 288, IR(S) 3400, 2900, 1550, 1310, ^{1}H n.m.r. 8.07 (1H,d,J=7.3 Hz,H-5), 8.00 (1H,br s,NH), 7.24-7.18 (2H,m,H-7 and H-8), 7.12 (1H,d,J=7.1 Hz,H-2), 6.92 (1H,d,J=7.1 Hz, H-3), 6.14 (1H,m,C<u>H</u>=CH$_2$), 5.30-5.20 (2H,m,CH=C<u>H</u>$_2$), 3.75 (2H,m,C<u>H</u>$_2$CH=CH$_2$), 2.84 (3H,s,4-CH$_3$), 2.52 (3H,s,1-CH$_3$), MS(<u>m/z</u>) 235(M$^+$, 100%), 220(40%) [Found: C, 86.7; H, 7.5; N, 5.9. $C_{17}H_{17}N$ requires: C, 86.8; H, 7.3; N, 5.95%].

Product B, 1,4-dimethyl-3-(prop-2-enyl)carbazole **139** (96 mg, 41%), m.p. 80-81 °C, UV 241, 250(sh), 262, 291, IR(S) 3400, 2900, 1590, 1320, ^{1}H n.m.r. 8.22 (1H,d,J=7.3 Hz,H-5), 7.88 (1H,br s,NH), 7.47-7.36 (2H,m,H-7 and H-8), 7.22 (1H,m,H-6), 7.03 (1H,s,H-2), 6.04 (1H,m,C<u>H</u>=CH$_2$), 5.08-4.93 (2H,m,CH=C<u>H</u>$_2$), 3.38-3.33 (2H,m,C<u>H</u>$_2$CH=CH$_2$), 2.78 (3H,s,4-CH$_3$), 2.48 (3H,s,1-CH$_3$), MS(<u>m/z</u>) 235(M$^+$, 100%), 220(55%) [Found: C, 86.7; H, 7.5; N, 5.8. $C_{17}H_{17}N$ requires: C, 86.8; H, 7.3; N, 5.95%].

<u>Rearrangement studies on 6-methoxy-1,4-dimethyl-9-(prop-2-enyl)carbazole</u> **132**:

(I) with aluminum trichloride in dichloromethane. — To an efficiently stirred solution of the dry carbazole 132 (5.3 g, 20 mmol) in dry dichloromethane (250 cm^3) at -30 °C,

a suspension of freshly ground aluminum trichloride (2.93 g, 22 mmol) in dry dichloromethane (10 cm^3) was added in very small portions. The resultant mixture was then warmed to room temperature (20 °C) gradually. After stirring for 7 h under nitrogen, the reaction mixture was quenched by being poured into a cold beaker of efficiently stirred water (250 cm^3). Stirring was continued for 30 min. The aqueous layer was extracted with dichloromethane (2x 100 cm^3). The combined organic layers were washed with water (3x 150 cm^3), saturated brine (150 cm^3), dried ($MgSO_4$) and the solvent removed to yield a colourless solid. Column chromatography on silica gel, eluting with dichloromethane (30%) in petroleum ether, afforded three products in the sequence A, B and C:

Product A, 6-methoxy-1,4-dimethyl-8-(prop-2-enyl)carbazole **134** (3.28 g, 62%), m.p. 119-120 °C, ^1H n.m.r. 7.82 (1H, br s,NH), 7.57 (1H,d,J=2.4 Hz,H-5), 7.09 (1H,d,J=7.4 Hz, H-7), 6.91 (1H,d,J=2.4 Hz,H-2), 6.89 (1H,d,J=7.4 Hz,H-3), 6.12 (1H,m,$C\underline{H}=CH_2$), 5.30-5.20 (2H,m,$CH=C\underline{H_2}$), 3.93 (3H,s, OCH_3), 3.70 (2H,d,J=6.2 Hz,$C\underline{H_2}CH=CH_2$), 2.83 (3H,s,4-CH_3), 2.50 (3H,s,1-CH_3), MS(m/z) 265(M^+, 100%), 250(60%), 224(10%) [Found: C, 81.7; H, 7.45; N, 5.2. $C_{18}H_{19}NO$ requires: C, 81.5; H, 7.2; N, 5.3%].

Product B, 8-(2-chloropropyl)-6-methoxy-1,4-dimethylcarbazole **156** (0.54 g, 9%), m.p. 120-121 °C, UV 234, 246, 255(sh), 265(sh), 295, IR(N) 3460, 1610, 1590, 1300, ^1H n.m.r. 7.86 (1H,br s,NH), 7.60 (1H,d,J=2.4 Hz,H-5), 7.11

(1H,d,J=7.3 Hz,H-2), 6.90 (1H,d,J=7.3 Hz,H-3), 6.89 (1H,d,J=2.4 Hz,H-7), 4.45 (1H,sextet,J=6.6 Hz,C<u>H</u>ClCH$_3$), 3.92 (3H,s,OCH$_3$), 3.42 (1H,dd,J=14.5, 6.6 Hz,C<u>H</u>(H)CHCl), 3.25 (1H,dd,J=14.5, 6.6 Hz,CH(<u>H</u>)CHCl), 2.82 (3H,s,4-CH$_3$), 2.54 (3H,s,1-CH$_3$), 1.59 (3H,d,J=6.6 Hz,C(H)ClC<u>H</u>$_3$), MS(<u>m/z</u>) 303 (19%), 301(M$^+$, 57%), 265(100%), 250(58%), 238(40%) [Found: C, 71.5; H, 6.6; N, 4.7. $C_{18}H_{20}ClNO$ requires: C, 71.6; H, 6.9; N, 4.6%].

Product C, 6-<u>methoxy</u>-1,4-<u>dimethyl</u>-3-(<u>prop</u>-2-<u>enyl</u>)<u>carbazole</u> **155** (1.27 g, 24%), m.p. 125-126 °C, ^{1}H n.m.r. 7.78 (1H,br s,NH), 7.75 (1H,d,J=2.6 Hz,H-5), 7.36 (1H,d,J=8.8 Hz, H-8), 7.05 (1H,dd,J=8.8, 2.6 Hz,H-7), 7.02 (1H,s,H-2), 6.03 (1H,m,C<u>H</u>=CH$_2$), 5.10-4.90 (2H,m,CH=C<u>H</u>$_2$), 3.93 (3H,s,OCH$_3$), 3.55 (2H,m,C<u>H</u>$_2$CH=CH$_2$), 2.77 (3H,s,4-CH$_3$), 2.49 (3H,s,1-CH$_3$), MS(<u>m/z</u>) 265(M$^+$, 100%), 250(67%), 225(37%), 149(37%) [Found: C, 81.4; H, 7.4; N, 5.15. $C_{18}H_{19}NO$ requires: C, 81.5; H, 7.2; N, 5.3%].

(II) with aluminum trichloride in nitromethane. — Aluminum trichloride (80 mg, 0.6 mmol) in nitromethane (3 cm^3) was added dropwise to a solution of the carbazole 132 (133 mg, 0.5 mmol) in nitromethane (7 cm^3) at -10 °C. After stirring at that temperature for 45 min, the resultant dark mixture was poured into water (50 cm^3) and extracted with ethyl acetate (3x 30cm^3). The combined organic layers were washed with saturated sodium hydrogen carbonate solution (30 cm^3), water (2x 30 cm^3), saturated brine

(30 cm^3), dried ($MgSO_4$), and the solvent removed to give a solid residue. Column chromatography on silica gel, eluting with dichloromethane$_{\wedge}^{(30\%)}$ in petroleum ether, afforded a colourless solid which was shown to be identical with 6-methoxy-1,4-dimethylcarbazole 138 (80 mg, 71%).

(III) with ethyl aluminum dichloride in dichloromethane. — A solution of ethyl aluminum dichloride (1 M, 0.6 cm^3) in hexane was added dropwise to a solution of the carbazole 132 (133 mg, 0.5 mmol) in dry dichloromethane (15 cm^3) at 0°C under nitrogen. The resultant mixture was stirred at room temperature for two days, however since tlc analysis showed that starting material was still present, the reaction mixture was then heated to reflux for 4 h. Even after this treatment, no new products formed in any significant amount.

(IV) with boron trichloride in dichloromethane. — A solution of boron trichloride (1 M, 0.6 cm^3) in dichloromethane was added dropwise to a solution of the carbazole 132 (133 mg, 0.5 mmol) in dry dichloromethane (8 cm^3) at -25°C under nitrogen. The reaction mixture was stirred for 11 h, but tlc analysis of the reaction mixture on silica gel indicated only the presence of the starting carbazole. The mixture was then stirred at room temperature for 20 h. Once more tlc analysis revealed that some of the starting carbazole remained together with a significant

amount of black material at the baseline of the tlc-plate.

(V) with zinc(II) chloride in xylene. — Zinc(II) chloride (83 mg, 0.6 mmol) was added to a solution of carbazole 132 (133 mg, 0.5 mmol) in dry xylene (10 cm^3) at 0°C. The resultant mixture was stirred at room temperature for 24 h before being heated under reflux for another 24 h. Tlc analysis of the reaction mixture concluded that starting carbazole remained in majority together with some very minor components.

(VI) with trifluoroacetic acid in dioxane. — A solution of carbazole 132 (133 mg, 0.5 mmol) in a mixture of trifluoroacetic acid (0.5 cm^3) and dioxane (5 cm^3) was stirred at room temperature for 24 h. Afterwards, tlc analysis indicated mainly the presence of unreacted carbazole.

Preparation of dimeric carbazoles 169 and 170. — Powdered aluminum trichloride (640 mg, 4.8 mmol), was added to a solution of carbazole 132 (1.06 g, 4 mmol) in dry dichloromethane (50 cm^3) at room temperature. After stirring for 5 h under nitrogen, the resultant mixture was poured into cold water (100 cm^3) and the aqueous layer was removed and extracted with dichloromethane (2x 50 cm^3). The combined organic layers were washed with water (2x 50 cm^3), brine (50 cm^3), dried ($MgSO_4$) and the solvent removed to give a

solid residue (890 mg). A fraction of the solid (100 mg) was chromatographed on silica gel, eluting with dichloromethane (5% to 45%) in petroleum ether to afford, in order, the following two products:

Product 169 (58 mg), m.p. decomp. 241-243 °C, UV 247, 258(sh), 268(sh), 299, IR(N) 3460, 1600, 1590, 1300, ^{1}H n.m.r.(A, denotes proton resonances belonging to the 8-unsubstituted carbazole unit and B, indicates protons resonances originating from the 8-substituted carbazole moiety.): 7.76 (A and B,2H,br s,2xNH, addition of d_6-DMSO caused this signal to resolve into two broad singlets at 10.08 and 9.44 ppm), 7.75 (A,1H,d,J=2.4 Hz,H-5), 7.62 (B,1H,d,J=2.4 Hz,H-5), 7.35 (A,1H,d,J=8.8 Hz,H-8), 7.27 (B,1H,s,H-2), 7.05 (A,1H,dd,J=8.8, 2.4 Hz,H-7), 6.99 (A,1H,s,H-2), 6.89 (B,1H,J=2.4 Hz,H-7), 6.11 (B,1H,m, C$\underline{H}$=CH$_2$), 5.28-5.19 (B,2H,m,CH=C$\underline{H}_2$), 3.93 (A,3H,s,OCH$_3$), 3.90 (B,3H,s,OCH$_3$), 3.69 (B,2H,m,C$\underline{H}_2$CH=CH$_2$), 3.54 (1H,m, C($\underline{H}$)CH$_3$), 3.14 (1H,dd,J=12.8, 5.3 Hz,C($\underline{H}$)HC(H)CH$_3$), 3.02 (1H,dd,J=12.8, 9.2 Hz,C(H)$\underline{H}$C(H)CH$_3$), 2.82 (B,3H,s, 4-CH$_3$), 2.74 (A,3H,s,4-CH$_3$), 2.55 (B,3H,s,1-CH$_3$), 2.45 (A,3H,s, 1-CH$_3$), 1.29 (3H,d,J=6.9 Hz,C(H)C$\underline{H}_3$), ^{13}C n.m.r. 152.3, 152.1, 137.8, 137.3, 135.5, 134.8, 134.5, 133.3, 128.3, 128.2, 127.0, 126.0, 123.8, 123.6, 123.5, 121.9, 120.7, 120.5, 116.8, 115.9, 115.1, 112.3, 112.1, 110.3, 105.5, 103.4, 55.2, 55.1, 40.9, 35.0, 34.8, 20.6, 16.4, 16.0, 15.4, 14.6, MS($\underline{m/z}$) 530(M$^+$, 17%), 380(7%), 307(3%), 292(100%), 238(24%) [Found: C, 81.3; H, 7.45; N, 5.0. $C_{36}H_{38}N_2O_2$

requires: C, 81.5; H, 7.2; N, 5.3%].

Product **170** (23 mg), m.p. decomp. 189-195°C, UV 247, 258(sh), 268(sh), 298, IR(N) 3460, 1600, 1590, 1300, ^{1}H n.m.r.(A, denotes proton resonances belonging to the 8-unsubstituted carbazole unit and B, indicates protons resonances originating from the 8-substituted carbazole moiety.): 7.79 (A and B,2H,br s,2xNH), 7.74 (A,1H,d,J=2.4 Hz,H-5), 7.64 (B,1H,d,J=2.2Hz,H-5), 7.33 (A,1H,d,J=8.6Hz, H-8), 7.29 (B,1H,s,H-2), 7.04 (A,1H,dd,J=8.6, 2.4 Hz,H-7), 7.00 (A,1H,s,H-2), 6.87 (B,1H,d,J=2.2 Hz,H-7), 4.45 (B,1H,m,C(Cl)$\underline{H}CH_3$), 3.93 (A,3H,s,OCH_3), 3.90(B,3H,s,OCH_3), 3.56 (1H,m,$CH_2C(\underline{H})CH_3$), 3.44 (B,1H,dd,J=15.4, 6.4 Hz, $C\underline{H}(H)C(Cl)H$), 3.26 (B,1H,dd,J=15.4, 6.4 Hz, $CH(\underline{H})C(Cl)H$), 3.17 (1H,dd,J=13.6, 9.1 Hz,$C\underline{H}(H)CH(CH_3)$), 3.04 (1H,dd, J=13.6, 5.4 Hz,$CH(\underline{H})CH(CH_3)$), 2.82 (B,3H,s,4-$CH_3$), 2.74 (A,3H,s,4-$CH_3$), 2.59 (B,3H,s,1-$CH_3$), 2.44 (A,3H,s,1-$CH_3$), 1.57 (B,3H,2d,J=6.4 Hz,$CH(Cl)C\underline{H}_3$), 1.27 (3H,d,J=6.9 Hz, $CH(C\underline{H}_3)$), MS(m/z) 568(3%), 566(M^+, 10%), 530(17%), 328(58%), 292(97%), 238(60%) [Found: C, 76.1; H, 5.5; N, 4.7. $C_{36}H_{39}ClN_2O_2$ requires: C, 76.2; H, 5.2; N, 4.9%].

Dehydrochlorination of 8-(2-chloropropyl)-6-methoxy-1,4-dimethylcarbazole **156**. — To a stirred solution of the carbazole 156 (1.5 g, 5 mmol) in dry dimethylformamide (25 cm^3) at 0°C, was added sodium hydride (0.44 g, 11 mmol, 60% in oil dispersion). The resultant mixture was stirred under nitrogen at room temperature for 15 h and then poured

into a beaker of cold stirred water (75 cm^3). The organic phase was separated and extracted with dichloromethane (2x 80 cm^3). The combined organic layers were washed with water (3x 80 cm^3), saturated brine (80cm^3), dried($MgSO_4$) and the solvent removed to give a solid residue. Column chromatography on silica gel, eluting with dichloromethane (30%) in petroleum ether, afforded a colourless solid (1.2 g, 91%) which was identical to 6-methoxy-1,4-dimethyl-8-(prop-2-enyl)-carbazole 134.

6-Methoxy-1,4-dimethyl-8-propenylcarbazole **168**.

— A solution of the carbazole 134 (4.5 g, 17 mmol) in dry benzene (100 cm^3) and bisacetonitrile palladium(II) chloride (0.5 g, 2 mmol) was stirred at 60 °C under nitrogen for 24 h. Benzene and the small amount of acetonitrile were evaporated off to give a dark residue which was subjected to column chromatography on silica gel, eluting with dichloromethane (30%) in petroleum ether. This afforded the title compound as a colourless solid (4.0 g, 89%), m.p. 138 °C, UV 210(sh), 235, 283, IR(N) 3360, 1610, 1590, 1310, ^1H n.m.r. 7.85 (1H,br s,NH), 7.56 (1H,d,J=2.4 Hz,5-H), 7.10 (1H,d, J=7.1 Hz,2-H), 7.06 (1H,d,J=2.4 Hz,7-H), 6.88 (1H,d,J=7.14 Hz,3-H), 6.73 (1H,dd,J=15.6, 1.8 Hz,C<u>H</u>=CH(CH_3)), 6.37 (1H,dq,J=15.6, 6.6 Hz,CH=C<u>H</u>(CH_3)), 3.93 (3H,s,OCH_3), 2.81 (3H,s,4-CH_3), 2.53 (3H,s,1-CH_3), 2.02 (3H,dd,J=6.6, 1.8 Hz, C(H)C<u>H</u>$_3$), MS(<u>m/z</u>) 265(M^+, 100%), 250(41%) [Found: C, 81.3; H, 7.4; N, 5.2. $C_{18}H_{19}NO$ requires: C, 81.5; H, 7.2; N,

5.3%].

1,4-Dimethyl-8-formylcarbazole **172**. — Into a stirred solution of propenylcarbazole 168 (5.31 g, 20 mmol) in a dry mixture of methanol (100 cm^3) and dichloromethane (100 cm^3) at -20 °C, was passed a stream of dry ozone gas, until no starting material remained (as indicated by tlc analysis). A stream of dry nitrogen gas was then bubbled through the reaction mixture for 5 min to extrude excess ozone and then dimethyl sulphide (2 cm^3) was added. After stirring at room temperature for 2 h, the solvent was removed from the resultant solution and column chromatography of the crude yellow residue on silica gel, eluting with ethyl acetate (10%) in petroleum ether then afforded the title compound as a yellow solid (4.0 g, 79%), m.p. 161 °C, UV 230, 264, 298, IR(N) 3350, 1670, 1613, 1584, 1300, ^{1}H n.m.r. 10.11 (1H,s,CHO), 9.88 (1H,br s,NH), 7.93 (1H,d,J=2.6 Hz,5-H), 7.36 (1H,d,J=2.6 Hz,7-H), 7.17 (1H,d, J=7.3 Hz,2-H), 6.95 (1H,d,J=7.3 Hz,3-H), 3.97 (1H,s,OCH_3), 2.80 (3H,s,4-CH_3), 2.56 (3H,s,1-CH_3), ^{13}C n.m.r. 193.1, 153.0, 140.0, 133.6, 130.9, 127.2, 126.7, 121.6, 121.5, 118.5, 118.1, 115.6, 115.4, 56.5, 20.4, 16.6, MS(m/z) 253(M^+, 100%), 238(97%) [Found: C, 75.9; H, 6.0; N, 5.4. $C_{16}H_{15}NO_2$ requires: C, 75.9; H, 6.0; N, 5.5%].

Trans-8-[3-(diethylamido)prop-2-enyl]-6-methoxy-1,4-dimethylcarbazole **174**. — A solution of diethyl

N,N-diethylphosphonoacetamide 173 (5.75 g, 21 mmol) in dry dimethylformamide (11 cm^3) was added dropwise to a stirred suspension of sodium hydride (1.67 g, 41.7 mmol, 60% oil dispersion) in dry dimethylformamide (160 cm^3) at 15 °C under nitrogen. Stirring was continued for 10 min after the addition. The reaction mixture was then cooled to 0 °C as a solution of formylcarbazole 172 (4.36 g, 17.2 mmol) in dry dimethylformamide (120 cm^3) was introduced. The resultant red solution was stirred at room temperature for 24 h until all the formylcarbazole had reacted. The reaction mixture was poured into cold water (500 cm^3) and extracted with ethyl acetate (4x 150 cm^3). The combined organic layers were washed with water (4x 150 cm^3), saturated brine (150 cm^3), dried ($MgSO_4$) and the solvent removed to give a solid residue. Column chromatography on silica gel, eluting with ethyl acetate in petroleum ether, afforded the title compound as a yellow solid (5.91 g, 98%) m.p. 207 °C, UV 238, 255(sh), 315, 410, IR(N) 3250, 1630, 1610, 1590, 1200, 980, ^1H n.m.r. 8.60 (1H,br s,NH), 8.21 (1H,d,J=15.2 Hz, C<u>H</u>=CHCONEt_2), 7.68 (1H,d,J=2.4 Hz,5-H), 7.24 (1H,d,J=2.4 Hz, 7-H), 7.11 (1H,d,J=7.2 Hz,2-H), 6.94 (1H,d,J=15.2 Hz, CH=C<u>H</u>CONEt_2), 6.89 (1H,d,J=7.2 Hz,3-H), 3.95 (3H,s,OCH_3), 3.53 (4H,m,N($C\underline{H}_2CH_3$)$_2$), 2.81 (3H,s,4-CH_3), 2.52 (3H,s, 1-CH_3), 1.30 (3H,t,J=7.1 Hz,$NCH_2C\underline{H}_3$), 1.21 (3H,t,J=7.1 Hz, $NCH_2.C\underline{H}_3$), Acc. MS(<u>m/z</u>) 350.197(M^+, 65.9%, calc. 350.199), 277.111(100%), 262.089(31.31%) [Found: C, 75.3; H, 7.6; N, 7.9. $C_{22}H_{26}N_2O_2$ requires: C, 75.4; H, 7.5; N, 8.0%].

Trans-8-[3-(diethylamido)prop-2-enyl]-3-formyl-6-methoxy-1,4-dimethylcarbazole **183**.– A dry 2-necked flask, fitted with a double surface water condenser was charged with a solution of imidazole (1.5 g, 22 mmol) in dry acetonitrile (120 cm^3). Freshly distilled trifluoroacetic anhydride (21.4 g, 102 mmol) was then added dropwise at room temperature. The mixture was bought to gentle reflux after the addition and while this reflux condition was maintained, a suspension of the carbazole 174 (5.91 g, 17 mmol) in dry acetonitrile (50 cm^3) was added. After heating under reflux for a further 3.5 h under nitrogen, the resultant brown solution was cooled to room temperature. The solvent was removed and the residue was dissolved in a mixture of sodium hydroxide/ ethanol/ water (15 g/300 cm^3/150 cm^3) at room temperature and stirred at 80 °C for 15 min. Most of the solvent was then removed and the residue was treated with water (150 cm^3) and extracted with ethyl acetate (4x 100 cm^3). The combined organic layers were washed with water (4x 80 cm^3), saturated brine (80 cm^3), dried ($MgSO_4$) and the solvent removed. Column chromatography of the crude residue on silica gel, eluting with ethyl acetate in petroleum ether, afforded the pure title compound as yellow prisms (5.3 g, 83%), m.p. 230 °C, UV 223, 253, 316, 380, IR(N) 3220, 1670, 1640, 1580, 970, ^1H n.m.r. 10.28 (1H,s,CHO), 9.58 (1H,s,NH), 8.25 (1H,d,J=15.4 Hz,C<u>H</u>=C(H)CONEt$_2$), 7.66 (1H,s, 2-H), 7.65 (1H,d,J=2.2 Hz,5-H), 7.19 (1H,d,J=2.2 Hz,7-H), 6.90 (1H,d,J=15.4 Hz,CH=C(<u>H</u>)CONEt$_2$), 3.94 (3H,s,OCH$_3$), 3.51

(4H,q,J=7.1 Hz,N(CH_2CH_3)2), 3.07 (3H,s,4-CH_3), 2.50 (3H,s, 1-CH_3), 1.30 (3H,t,J=7.1 Hz,NCH_2CH_3), 1.18 (3H,t,J=7.1 Hz, NCH_2CH_3), ^{13}C n.m.r. 191.5, 166.1, 154.1, 143.1, 136.9, 136.5, 134.4, 129.2, 126.4, 125.8, 121.8, 119.5, 118.8, 118.4, 110.1, 108.5, 56.2, 42.5, 41.3, 16.6, 15.1, 14.9, 13.2, MS(m/z) 378(M^+, 7%), 347(14%), 305(13%), 289(17%) [Found: C, 73.1; H, 7.1; N, 7.4. $C_{23}H_{26}N_2O_3$ requires: C, 73.0; H, 6.9; N, 7.4%].

Formylation of 8-[3-(Diethylamido)propyl]-1,4-dimethyl-6-methoxycarbazole 171. — The same procedure as described in the previous experiment was used with 8-[3-(diethylamido)propyl]-1,4-dimethyl-6-methoxycarbazole 171 as substrate. Two products, A and B were obtained in the ratio 4:1 :

Product A, 8-[3-(Diethylamido)propyl]-1,4-dimethyl-3-formyl-6-methoxycarbazole 180. Its ^1H n.m.r. spectroscopic data is the same as those given in the next experiment.

Product B, 8-[3-(Diethylamido)propyl]-3,7-diformyl-1,4-dimethyl-6-methoxycarbazole 181. ^1H n.m.r. 11.30 (1H,br s,NH), 10.76 and 10.42(2H,2s,7-CHO and 3-CHO), 7.76 (1H,s, H-2), 7.68 (1H,s,H-5), 4.05 (3H,s,OCH_3), 3.68 (2H,m, $CH_2CH_2CONEt_2$), 3.37 (2H,q,NCH_2CH_3), 3.22 (2H,q, NCH_2CH_3), 3.18 (3H,s,4-CH_3), 2.92 (2H,m,CH_2CH_2CONEt), 2.67 (3H,s, 1-CH_3), 1.02 (6H,t,2xNCH_2CH_3), MS(m/z) 408(M^+).

8-[3-(Diethylamido)propyl]-1,4-dimethyl-3-formyl-6-

methoxycarbazole **180**. — A solution of the carbazole 183 (5.14 g, 13.6 mmol) in ethyl acetate (300 cm^3), in the presence of palladium (0.5 g, 10% w/w on activated carbon) was hydrogenated at atmospheric pressure and at room temperature until no starting material remained. The reaction mixture was filtered through a pad of celite to remove the catalyst. The filtrate was evaporated to give a solid residue which after column chromatography on silica gel, eluting with ethyl acetate (25%) in petroleum ether, afforded the title compound as a pale yellow solid (4.27 g, 82%), m.p. 162 °C, UV 229, 251, 278, 297, 336, IR(S) 3230, 2920, 2850, 1730, 1660, 1620, 1030, ^{1}H n.m.r. 10.68 (1H,br s,NH), 10.42 (1H,s,CHO), 7.71 (1H,s,2-H), 7.63 (1H,d,J=2.6 Hz,5-H), 6.91 (1H,d,J=2.6 Hz,7-H), 3.94 (3H,s,OCH_3), 3.37 (4H,m, NCH_2CH_3 and $CH_2CH_2CONEt_2$), 3.22 (2H,q,J=7.3 Hz,NCH_2CH_3), 3.17 (3H,s,4-CH_3), 2.77 (2H,m,$CH_2CH_2CONEt_2$), 2.62 (3H,s,1-CH_3), 1.02 (6H,t,J=7.33 Hz,$N(CH_2CH_3)_2$), Acc. MS(m/z) 380.209(M^+, 100%; calc. 380.210), 307.121(53.53%) [Found: C, 72.8; H, 7.55; N, 7.3. $C_{23}H_{28}N_2O_3$ requires: C, 72.6; H, 7.4; N, 7.4%].

8-[3-(Diethylamido)propyl]-1,4-dimethyl-6-methoxy-carbazole **171**. — The same procedure as described in the previous experiment was used now at 60 psi, with 8-[3-(diethylamido)propenyl]-6-methoxy-1,4-dimethylcarbazole 174 (3.51 g, 10 mmol) as substrate. The title compound was thus obtained as a colourless solid (3.63 g, 97%),

m.p. 120 °C, UV 235, 245, 255(sh), 294, IR(S) 3270, 1610, 1600, 1300, 820, ^{1}H n.m.r. 9.84 (1H,br s,NH), 7.54 (1H,d, J=2.4 Hz,5-H), 7.07 (1H,d,J=7.3 Hz,2-H), 6.86 (1H,d, J=2.4 Hz,7-H), 6.84 (1H,d,J=7.3 Hz,3-H), 3.91 (3H,s,OCH_3), 3.34 (2H,m,$C\underline{H}_2CH_2CONEt_2$), 3.33 (2H,q,J=7.1 Hz,$NC\underline{H}_2CH_3$), 3.14 (2H,q,J=7.1 Hz,$NC\underline{H}_2CH_3$), 2.82 (3H,s,4-$CH_3$), 2.72 (2H,m, $CH_2C\underline{H}_2CONEt_2$), 2.58 (3H,s,1-$CH_3$), 1.00 (3H,t,J=7.1 Hz, $NCH_2C\underline{H}_3$), 0.96 (3H,t,J=7.1 Hz,$NCH_2C\underline{H}_3$), MS(m/z) 352(M^+, 100%), 306(10%), 279(78%), 264(12%) [Found: C, 74.8; H, 8.2; N, 7.9. $C_{22}H_{28}N_2O_2$ requires: C, 75.0; H, 8.0; N, 7.95%].

8-[3-(Diethylamido)propyl]-1,4-dimethyl-3-[N-(2,2-dimethoxy)ethylaminomethyl]-6-methoxycarbazole **185**. — A mixture of the formylcarbazole 180 (1.9 g, 5 mmol) and excess dry aminoacetaldehyde dimethyl acetal (5.0 g), in the presence of activated molecular sieves (4A) was heated at 80 °C until all the formyl compound had reacted (as indicated by tlc analysis on neutral alumina plates). Most of the remaining acetal reagent was removed under reduced pressure (0.05 mm Hg) at ambient temperature. The residue was dissolved in absolute ethanol (120 cm^3) and was then hydrogenated, in the presence of platinum(IV) oxide (0.2 g), at atmospheric pressure and room temperature for 4 h. The hydrogenation mixture was filtered through a pad of celite to remove the catalyst and the filtrate evaporated to dryness to afford the title compound as a colourless solid (2.1 g, 90%). This was carried through without

characterisation to the next stage.

8-[3-(Diethylamido)propyl]-1,4-dimethyl-3-[N-(2,2-dimethoxy)ethyl-N-tosyl-aminomethyl]-6-methoxycarbazole **186**. — To a stirred solution of the aminomethylcarbazole 185 (2.1 g, 4.5 mmol) in dry pyridine (50 cm^3) at 0 °C, was added freshly recrystallised tosyl chloride (1.02 g, 5.4 mmol). After stirring at room temperature for 24 h, the resultant brown solution was poured into water (200 cm^3) and extracted with ethyl acetate (3x 80 cm^3). The combined organic layers were washed successively with hydrochloric acid (0.5 M, 3x 80 cm^3), saturated sodium hydrogen carbonate solution (120 cm), water (2x 80 cm^3), saturated brine (80 cm^3), dried ($MgSO_4$) and the solvent removed. Column chromatography of the residue on silica gel, eluting with ethyl acetate in petroleum ether, afforded the title compound as colourless plates (2.38 g, 85%), m.p. 174 °C, UV 238, 246(sh), 268, 297, IR(N) 3300, 1615, 1590, 1160, ^1H n.m.r. 9.91 (1H,br s,NH), 7.75 (2H,d,J=8.3 Hz,Tosyl-Hs), 7.59 (1H,d,J=2.5 Hz,5-H), 7.30 (2H,d,J=8.3 Hz,Tosyl-Hs), 6.88 (1H,s,2-H), 6.87 (1H,d,J=2.5 Hz,7-H), 4,58 (2H,s,3-CH_2N), 4.13 (1H,t,J=5.5 Hz,$CH(OMe)_2$), 3.91 (3H,s,6-OCH_3), 3.35 (2H,q,J=7.1 Hz, $NC\underline{H}_2CH_3$), 3.34 (2H,m,$C\underline{H}_2CH_2CONEt_2$), 3.20 (2H,q,J=7.1 Hz, $NC\underline{H}_2CH_3$), 3.16 (2H,d,J=5.5 Hz,$C\underline{H}_2CH(OMe)_2$), 3.12 (6H,s, $CH(OC\underline{H}_3)_2$), 2.81 (3H,s,4-CH_3), 2.75 (2H,m,$CH_2C\underline{H}_2CONEt_2$), 2.48 (3H,s,1-$CH_3$), 2.42 (3H,s,$SO_2C_6H_4C\underline{H}_3$), 1.00 (6H,t,

J=7.1 Hz,N($CH_2\underline{C}H_3$)$_2$), MS(m/z) 623(M^+), 366(100%), 293(77%), 278(20%), 250(20%) [Found: C, 65.3; H, 7.4; N, 6.7. $C_{34}H_{45}N_3O_6S$ requires: C, 65.5; H, 7.3; N, 6.7%].

7-[3-(Diethylamido)propyl]-9-methoxyellipticine

187. — Concentrated hydrochloric acid (10 M, 1.0 cm^3) was added to a stirred solution of the carbazole 186 (320 mg, 0.5 mmol) in dioxane (20 cm^3) at room temperature under nitrogen. The mixture was stirred at 100 °C for 3 h and then cooled to room temperature, diluted with water (40 cm^3) and basified with concentrated ammonium hydroxide solution before being extracted with ethyl acetate (3x 40 cm^3). The combined organic layers were washed with water (2x 50 cm^3), brine (50 cm^3) and the solvent was removed to give a yellow residue. Column chromatography on silica gel, eluting with ethyl acetate$_{\wedge}^{(55\%)}$in petroleum ether, afforded the title compound as a yellow solid (116 mg, 56%), m.p. 163 °C, UV 210(30200), 243(26800), 296(62800), 337(6260), 410(4100), IR(N) 3280, 1600, ^{1}H n.m.r. 10.32 (1H,br s,NH), 9.68 (1H,s, 1-H), 8.45 (1H,d,J=6.2 Hz,3-H), 7.85 (1H,dd,J=6.2, 0.6 Hz, 4-H), 7.75 (1H,d,J=2.4 Hz,10-H), 6.97 (1H,d,J=2.4 Hz,8-H), 3.96 (3H,s,OCH_3), 3.38 (2H,m,$C\underline{H}_2CH_2CONEt_2$), 3.37 (2H,q, J=7.14 Hz,$NC\underline{H}_2CH_3$), 3.26 (3H,s,11-CH_3), 3.21 (2H,q,J=7.14 Hz,$NC\underline{H}_2CH_3$), 2.84 (3H,d,J=0.6 Hz,5-CH_3), 2.79 (2H,m, $CH_2C\underline{H}_2CONEt_3$), 1.00 (6H,t,J=7.14 Hz,N($CH_2\underline{C}H_3$)2), Acc. MS (m/z) 403.221(M^+, 100%, calc. 403.226), 386(4.7%), 368(28%), 353(3%), 348(8.1%), 330(50.7%) [Found: C, 74.6; H, 7.35; N,

10.4. $C_{25}H_{29}N_3O_2$ requires: C, 74.4; H, 7.2; N, 10.4%].

7-[3-(Diethylamino)propyl]-9-methoxyellipticine

117. — A solution of borane-methyl sulphide complex in tetrahydrofuran (2 M, 0.55 cm^3) was added dropwise to a dry solution of the ellipticine 187 (114 mg, 0.28 mmol) in tetrahydrofuran (6 cm^3) under nitrogen, heated under reflux. After 75 min, hydrochloric acid (6 M, 1 cm^3) was added and the resultant solution heated for a further 15 min. It was then cooled to room temperature and the solvent removed to give a residue which was treated with water (20 cm^3), basified with ammonium hydroxide solution and the solution extracted with ethyl acetate (3x 20 cm^3). The combined organic layers were washed with water (2x 15 cm^3) and brine (20 cm^3), and the solvent removed to give an oily residue. Column chromatography on silica gel, eluting with triethylamine/ ethyl acetate/ petroleum ether (0.5:75:25), then afforded the title compound as an orange viscous oil (56 mg, 51%), UV 210(29860), 243(32030), 296(61840), 405(3980), IR(N) 3250, 1610, ^1H n.m.r. 10.25 (1H,br s,NH), 9.59 (1H,s,1-H), 8.37 (1H,d,J=6.1 Hz,3-H), 7.72 (1H,d, J=6.1 Hz,4-H), 7.64 (1H,d,J=2.4 Hz,10-H), 6.89 (1H,d,J=2.4 Hz,8-H), 3.88 (3H,s,OCH_3), 3.15 (3H,s,11-CH_3), 2.94 (2H, br t,J=6.7 Hz,$C\underline{H}_2(CH_2)_2NEt_2$), 2.68 (3H,s,5-$CH_3$), 2.58 (4H,q,J=7.14 Hz,$N(C\underline{H}_2CH_3)_2$), 2.32 (2H,br t,J=6.7 Hz, $C\underline{H}_2NEt_2$), 1.93 (2H,m,$C\underline{H}_2CH_2NEt_2$), 0.94 (6H,t,J=7.14 Hz, $N(CH_2C\underline{H}_3)_2$), ^{13}C n.m.r. 154.1, 149.9, 142.2, 140.5, 137.8,

133.1, 128.5, 125.1, 124.9, 124.6, 122.3, 115.9, 115.2, 108.4, 106.1, 56.2, 50.0, 46.3, 28.2, 28.0, 14.4, 12.3, 10.4, Acc. MS(m/z) 389.248(M^+, 100%, calc. 389.246), 316.157(35.5%), 290.141(80.0%) [Found: C, 77.0; H, 8.2; N, 10.7. $C_{25}H_{31}N_3O$ requires: C, 77.1; H, 8.0; N, 10.8%].

N,N-Diethylchloroacetamide 176. — Chloroacetyl chloride (28.4 g, 250 mmol) at 0°C was added dropwise to a vigorously stirred solution of diethylamine (36.5 g, 500 mmol) in dry ether (75 cm^3) at 0°C. The mixture was stirred overnight (15 h) at room temperature and then diluted with dichloromethane (150 cm^3) and washed successively with hydrochloric acid (2 M, 80 cm^3), saturated sodium hydrogen carbonate solution (80 cm^3), water (2x 80 cm^3) and brine (80 cm^3). After drying ($MgSO_4$), the solvent was removed to give an oily residue, distillation of which afforded the title compound as a colourles oil (25.4 g, 68%), b.p. 82°C/0.1 mm Hg, IR(L) 1650, ^1H n.m.r. (60 MHz) 4.10 (2H,s,$ClCH_2$), 3.40 (4H,q,J=7.1 Hz, $N(C\underline{H}_2CH_3)_2$), 1.18 (6H,t,J=7.1 Hz,$N(CH_2C\underline{H}_3)_2$).

Diethyl N,N-diethylaminocarbonylmethylphosphonate 173 — Triethyl phosphite (10.0 g, 60 mmol) and N,N-diethyl chloroacetamide 176 (7.5 g, 50 mmol) was stirred at 150°C for 2.5 h and the reaction mixture then distilled under reduced pressure to afford the title compound as a colourless oil (9.5 g, 75%), b.p. 166°C/0.04 mm Hg), IR(L)

1640, ^{1}H n.m.r.(60 MHz) 4.21 (4H,m,($OC\underline{H}_2CH_3$)$_2$), 3.45 (4H,m, ($NC\underline{H}_2CH_3$)$_2$), 3.02 (2H,d,J=22 Hz,$P(O)CH_2$), 1.45-1.00(12H,m, ($OCH_2C\underline{H}_3$)$_2$ and N($CH_2C\underline{H}_3$)$_2$).

8-[3-(Diethylamido)propenyl]-1,4-dimethyl-3-[N-(2,2-dimethoxy)ethyliminomethylidene]-6-methoxycarbazole

188. — A mixture of the formylcarbazole 183 (95 mg, 0.25 mmol) and excess dry aminoacetaldehyde dimethyl acetal (0.25 g), in the presence of activated molecular sieves (4A) was heated at 80°C until all the formyl compound had reacted, as indicated by tlc analysis (on neutral alumina). The remaining acetal was removed under reduced pressure (0.05 mm Hg) at room temperature and the residue crystallised from benzene to yield the title compound as yellow prisms (69 mg, 73%), m.p. 181°C, UV 227(sh), 256, 315, 400, IR(S) 3320, 1640, 1610, 1590, 1130, ^{1}H n.m.r. 8.83 (2H,br s,NH and CH=N), 8.21 (1H,d,J=15.2 Hz,$C\underline{H}$=C(H)$CONEt_2$), 7.89 (1H,s,2-H), 7.75 (1H,d,J=2.2 Hz,5-H), 7.25 (1H,d,J=2.2 Hz,7-H), 6.94 (1H,d,J=15.2 Hz,CH=C($\underline{H}$)$CONEt_2$), 4.74 (1H, t,J=5.6 Hz,$CH(OMe)_2$), 3.96 (3H,s,OCH_3), 3.84 (2H,dd,J=5.6, 1.1 Hz,$NC\underline{H}_2CH(OMe)_2$), 3.53 (4H,m,($NC\underline{H}_2CH_3$)$_2$), 3.46 (6H, s,$CH(OC\underline{H}_3)_2$), 2.95 (3H,s,4-$CH_3$), 2.53 (3H,s,1-$CH_3$), 1.31 (3H,t,J=7.15 Hz,$NCH_2C\underline{H}_3$), 1.22 (3H,t,J=7.15 Hz, $NCH_2C\underline{H}_3$), MS(m/z) 465(M^+, 27%), 434(4%), 390(19%), 75(100%) [Found: C, 69.6; H,7.8; N, 8.95. $C_{27}H_{35}N_3O_4$ requires: C, 69.7; H,7.6; N, 9.0%].

8-[3-(Diethylamido)propenyl]-1,4-dimethyl-3-[N-(2,2-dimethoxy)ethylaminomethyl]-6-methoxycarbazole **189**. — Sodium borohydride (12.5 mg, 0.33 mmol) was added to a solution of the Schiff's base 188 (51 mg, 0.11 mmol) in ethanol (10 cm^3) at 5°C. The progress of the reaction was followed by studying the UV spectra of the reaction mixture at 20 min intervals and when no further changes was noted in the peak at max 314 nm, it was quenched by pouring the reaction mixture into water (30 cm^3). The volume of this mixture was reduced by about 50% and it was then extracted with ethyl acetate (2x 30 cm^3). The combined organic layers were washed with water (2x 20 cm^3), brine, dried ($MgSO_4$) and the solvent removed to afford a yellow solid (46.5 mg, 91%) which was sufficiently pure for the next step. UV 244, 260(sh), 402, IR(N) 3260, 1630, 1590, ^1H n.m.r. 8.48 (1H,br s,NH), 8.19 (1H,d, J=15.2 Hz,C<u>H</u>=C(H)CONEt$_2$), 7.75 (1H,d,J=2.2 Hz,5-H), 7.24 (1H,d,J=2.2 Hz,7-H), 7.17 (1H,s,2-H), 6.95 (1H,d,J=15.2 Hz, CH=C(<u>H</u>)CONEt$_2$), 4.53 (1H,t,J=5.6 Hz,CH(OMe)$_2$), 3.96 (5H, s,6-OCH_3 and 3-CH_2NH), 3.52 (4H,m,N(C<u>H</u>$_2$CH$_3$)$_2$), 3.37 (6H,s, CH(OC<u>H</u>$_3$)$_2$), 2.84 (2H,d,J=5.6 Hz,C<u>H</u>$_2$CH(OMe)$_2$), 2.82 (3H, s,4-CH_3), 2.51 (3H,s,1-CH_3), 1.90 (1H,br s,3-CH_2N<u>H</u>), 1.30 (3H,t,J=7.15 Hz, NCH$_2$C<u>H</u>$_3$), 1.21 (3H,t,J=7.15 Hz,NCH$_2$C<u>H</u>$_3$).

8-[3-(Diethylamido)propenyl]-1,4-dimethyl-3-[N-(2,2-dimethoxy)ethyl-N-tosyl aminomethyl]-6-methoxycarbazole **190**. — Freshly recrystallised tosyl chloride (21.2 mg,

0.11 mmol) was added to a stirred solution of the aminomethylcarbazole 189 (40 mg, 0.086 mmol) in dry pyridine (10 cm^3) at 0 °C. After stirring at room temperature for 24 h, the restultant brown solution was poured into water (40 cm^3) and extracted with ethyl acetate (3x 20 cm^3). The combined organic layers were washed successively with hydrochloric acid (0.5 M, 3x 20 cm^3), saturated sodium hydrogen carbonate solution (2x 20 cm^3), water (2x 20 cm^3), saturated brine (20 cm^3), dried ($MgSO_4$) and the solvent removed to give a solid residue. Column chromatography of which on silica gel, eluting with ethyl acetate (35%) in petroleum ether, afforded the title compound as yellow prisms (49 mg, 92%), UV 244, 261(sh), 317, 400, IR(N) 3300, 1640, 1590, 1320, 1150, 970, MS(m/z) 621(M^+), 364, 291.

Attempted preparation of 7-[3-(diethylamido)propenyl]-9-methoxyellipticine **191**. — To a stirred solution of the carbazole 190 (20 mg) in dioxane (4 cm^3) at room temperature under nitrogen was added concentrated hydrochloric acid (10 M, 0.1 cm^3) was added. After stirring at 100 °C for 24 h, the mixture was cooled to room temperature, diluted with water (10 cm^3) and basified with concentrated ammonium hydroxide solution. This mixture was extracted with ethyl acetate (3x 10 cm^3) and the combined organic layers were washed with water (2x 10 cm^3), saturated brine (10 cm^3), dried ($MgSO_4$) and the solvent removed. Tlc analysis of the yellow residue which remained indicated the

presence of many components. ^{1}H n.m.r. analysis of the crude residue, however, suggested there was no ellipticine like product had formed.

Catalytic reduction of 8-[3-(diethylaimdo)propenyl]-1,4-dimethyl-3-[N-(2,2-dimethoxy)ethyl-N-tosyl-aminomethyl]-6-methoxycarbazole **190**.— A solution of the propenylcarbazole 190 (20 mg) in ethyl acetate (20 cm^3), in the presence of palladium (2 mg, 10% on activated carbon), was hydrogenated at atmospheric pressure and room temperature. The reaction mixture was filtered through a bed of celite to remove the catalyst and the filtrate was evaporated to dryness to give a colourless residue. Column chromatography on silica gel, eluting with ethyl acetate in petroleum ether, afforded a product which was identical with the propylcarbazole 186 in all respects (19.6 mg, 98%).

Claisen rearrangement of 1,4-dimethyl-6-(prop-2-enyloxy)carbazole **192** under thermal conditions. — A solution of carbazole 192 (0.5 g, 2 mmol) in xylene (20 cm^3) was heated to reflux for 60 h, then cooled and the solvent removed. Column chromatography of the residue on neutral alumina, eluting with dichloromethane in petroleum ether, afforded 1,4-dimethyl-6-hydroxy-5-(prop-2-enyl)carbazole **195**, a colourless solid (0.4 g, 80%), as the only product, UV 243, 250, 260(sh), 298, IR(N) 3420, 3380, 1600, 1210, 1170, ^{1}H n.m.r.(d_6-Acetone) 10.12 (1H,br s,NH), 7.72

(1H,br s,OH), 7.29 (1H,d,J=8.4 Hz,8-H), 7.05 (1H,d,J=8.4 Hz,7-H), 7.02 (1H,d,J=7.3 Hz,2-H), 6.81 (1H,d,J=7.3 Hz, 3-H), 6.20 (1H,m,C<u>H</u>=CH_2), 5.05-4.25 (2H,m,CH=C<u>H_2</u>), 4.12 (2H,m,C<u>H_2</u>CH=CH_2), 2.93 (3H,s,4-CH_3), 2.49 (3H,s,1-CH_3).

<u>Claisen rearrangement of 1,4-dimethyl-6-(prop-2-enyloxy)carbazole 192 in the presence of boron trichloride</u>. — To a solution of carbazole 192 (1.29 g, 5 mmol) in dry dichloromethane (80 cm^3) below -25°C, was added dropwise boron trichloride (1 M, 6 cm^3) in dichloromethane. After stirring at that temperature for 35 min, the mixture was poured into cold water (100 cm^3) and the aqueous phase was collectedand extracted with dichloromethane (2x 40 cm^3). The combined organic layers were washed successively with saturated sodium hydrogen carbonate solution (50 cm^3), water (2x 50 cm^3), brine (50 cm^3), dried ($MgSO_4$) and the solvent removed to give a solid residue. Column chromatography on flash silica, eluting with ethyl acetate (35%) in petroleum ether, afforded two products A and B:

Product A (0.15 g, 12%), was shown to be 1,4-<u>dimethyl</u>-6-<u>hydroxy</u>-7-(<u>prop</u>-2-<u>enyl</u>)<u>carbazole</u> 196, IR(S) 3440, 3300, 1610, 1300, ^1H n.m.r. 7.78 (1H,s,NH), 7.61 (1H,s,5-H), 7.20 (1H,s,8-H), 7.08 (1H,d,J=7.3 Hz,2-H), 6.87 (1H,d,J=7.3 Hz, 3-H), 6.09 (1H,m,C<u>H</u>=CH_2), 5.18 (2H,m,CH=C<u>H_2</u>), 4.87 (1H, s,OH), 3.57 (2H,m,C<u>H_2</u>CH=CH_2), 2.78 (3H,s,4-CH_3), 2.49 (3H, s,1-CH_3), ^{13}C n.m.r. 147.7, 139.4, 136.7, 134.6, 130.6,

125.9, 124.2, 123.7, 121.0, 120.4, 117.0, 116.4, 111.4, 108.8, 35.8, 20.3, 16.6.

Product B (1.07 g, 83%), was the major isomer and found to be identical with 1,4-dimethyl-6-hydroxy-5-(prop-2-enyl) carbazole 195.

6-Methoxy-1,4-dimethyl-7-(prop-2-enyl)carbazole

168. — A mixture of hydroxycarbazole 196 (251 mg, 1 mmol), benzyl triethylammonium bromide (687 mg, 2.5 mmol), methyl iodide (340 mg, 2.4 mmol), sodium hydroxide (100 mg, 2.5 mmol) in dichloromethane (30 cm^3) and water (15 cm^3) was stirred vigorously under nitrogen for six days. The mixture was allowed to separate into two layers. The aqueous layer was collected and extracted with dichloromethane (2x 50 cm^3). The combined organic layers were then washed with water (2x 40 cm^3), saturated brine (40 cm^3), dried ($MgSO_4$) and the solvent removed to give a solid residue. This after column chromatography on silica gel, eluting with dichloromethane in petroleum ether, afforded the title compound as colourless plates (236 mg, 89%), m.p. 110-111 °C, UV 236, 243(sh), 254(sh), 265, IR(N) 3370, 1630, 1570, 1200, ^1H n.m.r. 7.72 (1H,br s,NH), 7.59 (1H,s,5-H), 7.20 (1H,s, 8-H), 7.06 (1H,d,J=7.2 Hz,2-H), 6.87 (1H,d,J=7.2 Hz,3-H), 6.09 (1H,m,C<u>H</u>=CH_2), 5.13-5.04 (2H,m,CH=C<u>H</u>$_2$), 3.93 (3H, s,OCH_3), 3.54 (2H,d,J=6.6 Hz,C<u>H</u>$_2$CH=CH_2), 2.82 (3H,s,4-CH_3), 2.46 (3H,s,1-CH_3), ^{13}C n.m.r. 151.9, 137.4, 134.3, 130.2, 127.6, 125.6,123.0, 121.7, 120.4, 117.1, 115.4, 111.4,

104.3, 56.3, 34.9, 20.4, 16.5, MS(m/z) 265(M^+, 100%), 250(25%), 235(27%) [Found: C, 81.5; H, 7.3; N, 5.2. $C_{18}H_{19}NO$ requires: C, 81.5; H, 7.22; N, 5.3%].

3-(2-Methoxy-5-nitrophenyl)prop-2-enoic acid **203**. — A mixture of 2-methoxy-5-nitrobenzaldehyde (18.1 g, 100 mmol) and 1,3-propanedioic acid (15.6 g, 150 mmol) in pyridine (50 cm^3) and piperidine (1 cm^3) were heated at 100 °C for 4 h. The mixture was cooled to room temperature and poured into a stirred mixture of hydrochloric acid (6 M, 70 cm^3) and crushed ice (ca. 70 g). After 15 min of stirring in the aqueous acid, the solid which had precipitated was filtered off and washed successively with dilute hydrochloric acid (2 M, 20 cm^3), cold water (3x 20 cm^3). Crystallisation from methanol afforded the title compound as colourless needles (18.7 g, 84%), m.p. 230 °C, IR(N) 3200-2600br, 1700, 1630, 1590, ^1H n.m.r.(d_6-DMSO, a peak corresponding to the resonance of the acidic proton was not observed in pure d_6-DMSO, but was when in a mixture of d_6-DMSO/$CDCl_3$: at 6.20 as a broad singlet) 8.35 (1H,d,J=2.7 Hz,6-H), 8.26 (1H,dd,J=8.5, 2.7 Hz,4-H), 7.75 (1H,d,J=16.5 Hz,C<u>H</u>=CHCO$_2$H), 7.30 (1H,d,J=8.5 Hz,3-H), 6.65 (1H,d,J=16.5 Hz,CH=C<u>H</u>CO$_2$H), 4.00 (3H,s,OCH_3), MS(m/z) 223(M^+, 86%), 193(90%), 192(100%).

3-(5-Amino-2-methoxyphenyl)prop-2-enoic acid **204**. — Nitrocinnamic acid 203 (1.0 g) in ethanol (20 cm^3), in

the presence of palladium (0.1 g, 10% on activated carbon) as catalyst was hydrogenated at atmospheric pressure and room temperature for 4 h. The reaction mixture was filtered through a bed of celite to remove the catalyst. The filtrate was evaporated to dryness to leave a crystalline residue which was recrystallised from ethanol to give the title compound as colourless plates (0.92 g, 91%), m.p. decomp. 276°C, IR(N) 2800-2400br, 1620, 1590, 1500, ^{1}H n.m.r. (d -DMSO) 6.80-6.30 (3H,m,Ar-Hs), 6.5-5.1(3H,very br s,NH3), 3.74 (3H,s,OCH_3), 2.60 (4H,m,$\underline{CH_2}\underline{CH_2}CO_2$), MS(m/z) 195($M^+$, 100%), 180(10%), 162(22%), 134(60%).

Diethyl 3-(2-methoxy-5-nitrophenyl)prop-2-enamide **205**. — Nitrocinnamic acid 203 (22.3 g, 100 mmol) in thionyl chloride (80 cm^3) was heated to reflux under a dry atmosphere for 3 h. Excess thionyl chloride was removed and the residue was dissolved in dry benzene (200 cm^3) and cooled to -10°C. Then freshly distilled triethylamine (26 cm^3, 250 mmol) was added dropwise. Stirring was continued while the reaction mixture was held at 0°C for 30 min before the temperature was raised to 60°C for 3 h. After removing the solvent, the residue was taken up in dichloromethane (200 cm^3) and washed successively with diluted hydrochloric acid (2 M, 100 cm^3), saturated sodium carbonate (100 cm^3), water (2x 100 cm^3), saturated brine (100 cm^3). After being dried ($MgSO_4$), the solvent was removed to yield a solid residue which crystallised from

ethyl acetate in petroleum ether, as colourless prisms (23 g, 83%), m.p. 100-101 °C, UV 275, 304(sh), IR(N) 1630, 1600, 1570, 1330, 1270, 1260, ^{1}H n.m.r. 8.39 (1H,d,J=2.8 Hz,6-H), 8.22 (1H,dd,J=9.0, 2.8 Hz,4-H), 7.96 (1H,d,J=15.6 Hz,C<u>H</u>=CHCONEt$_2$), 6.99 (1H,d,J=9.0 Hz,3-H), 6.98 (1H,d,J=15.6 Hz,CH=C<u>H</u>CONEt$_2$), 3.99 (3H,s,OCH$_3$), 3.51 (4H,m,N(C<u>H</u>$_2$CH$_3$)$_2$), 1.25 (6H,m,N(CH$_2$C<u>H</u>$_3$)$_2$), MS(<u>m/z</u>) 278(20%), 247(37%), 206(100%), 190(39%).

<u>Diethyl 3-(5-amino-2-methoxyphenyl)propionamide</u> **206**. — A solution of the unsaturated nitroamide 205 (20 g) in ethyl acetate (200 cm^3), in the presence of palladium (2 g, 10% on activated carbon) as catalyst was hydrogenated at atmospheric pressure, in the dark. The solution was filtered through a bed of celite to removed the catalyst and the filtrate was evaporated to dryness to afford an amber oil (17.6 g, 98%), IR(L) 3450, 3300, 3250, 3000, 1760, 1620, ^{1}H n.m.r. 6.70-6.50 (3H,m,Ar-Hs), 3.78 (3H,s,OCH$_3$), 3.62 (2H,s,NH$_2$), 3.47 (4H,m,N(C<u>H</u>$_2$CH$_3$)$_2$), 2.81 (4H,m,C<u>H</u>$_2$C<u>H</u>$_2$CONEt$_2$), 1.20 (6H,m,N(CH$_2$C<u>H</u>$_3$)$_2$), MS(<u>m/z</u>) 250(M$^+$, 100%), 223(15%), 219(20%), 72(21%)

<u>Diethyl 3-(2-methoxy-5-methylsulphonylaminophenyl)-propionamide</u> **207**. — Dry pyridine (30 cm^3) was added dropwise to a solution of amide 206 (12 g, 48 mmol) in dry dichloromethane (120 cm^3) at 0 °C. This was followed by the introduction of methylsulphonyl chloride (7.15 g,

62.4 mmol). The reaction mixture was stirred at room temperature for 24 h and then poured into water (100 cm^3). The aqueous phase extracted with dichloromethane (2x 60 cm^3) and the combined organic layers were washed successively with diluted hydrochloric acid (2 M, 80 cm^3), saturated sodium hydrogen carbonate (80 cm^3), water (2x 80 cm^3), saturated brine (100 cm^3), dried ($MgSO_4$) and evaporated. The residue was crystallised from ethyl acetate in petroleum ether, to afford the title compound as a colourless solid (12.9 g, 82%), m.p. 166°C, UV 234, 283, IR(S) 3280, 1630, 1330, 1150, ^1H n.m.r. 8.81 (1H,br s,NH), 7.15 (1H,dd,J=8.6, 2.7 Hz,6-H), 7.11 (1H,d,J=2.7 Hz,2-H), 6.80 (1H,d,J=8.6 Hz, 5-H), 3.81 (3H,s,OCH_3), 3.34 (4H,m,$N(CH_2CH_3)_2$), 2.90 (2H, m,$CH_2CH_2CONEt_2$), 2.89 (3H,s,SO_2CH_3), 2.55 (2H,m, $CH_2CH_2CONEt_2$), 1.12 (6H,m,$N(CH_2CH_3)_2$), MS(m/z) 328(M^+, 97%), 297(11%), 249(90%), 222(6%), 100(100%) [Found: C, 54.7; H,7.55; N, 8.4. $C_{15}H_{24}N_2O_4S$ requires: C, 54.9; H,7.4; N, 8.5%].

Diethyl 3-[5-(2,2-diethoxyethyl)methylsulphonylamino-2-methoxyphenyl]-propionamide **201**. — A solution of the sulphonamide 207 (3.28 g, 100 mmol) in dry dimethylformamide (25 cm^3) was added dropwise to a stirred suspension of sodium hydride (0.48 g, 60% in oil dispersion) in dry dimethylformamide (10 cm^3) at room temperature under nitrogen. The solution was stirred at room temperature for 15 min and then cooled to 0°C. A solution of

2-bromo-1,1-diethoxyethane (23.6 g, 120 mmol) in dry dimethylformamide (5 cm^3) was then added. The resultant mixture was stirred at room temperature for 15 min and then at 100 °C for 4 h. It was allowed to cool, poured into water (250 cm^3) and extracted with ethyl acetate (3x 100 cm^3). The combined organic extract was washed with water (3x 100 cm^3), saturated brine (100 cm^3), dried ($MgSO_4$) and the solvent removed to yield a solid residue. Column chromatography of which on silica gel, eluting with ethyl acetate (65%) in petroleum ether, afforded the title compound as a colourless oil (3.37 g, 76%), IR(L) 3000, 2800, 1640, 1510, 1350, ^1H n.m.r. 7.42-6.85 (3H,m,Ar-Hs), 4.66 (1H,t,J=6.2 Hz, $CH(OEt)_2$), 3.86 (3H,s,OCH_3), 3.61 (4H,m,$O(C\underline{H}_2CH_3)_2$), 3.34 (4H,m,$N(C\underline{H}_2CH_3)_2$), 3.30 (2H,d,J=6.2 Hz,$C\underline{H}_2CH(OEt)_2$), 3.08(3H,s,$SO_2CH_3$), 2.97 (2H,m,$C\underline{H}_2CH_2CONEt_2$), 2.68 (2H,m, $CH_2C\underline{H}_2CONEt_2$), 1.10 (12H,m,$N(CH_2C\underline{H}_3)_2$ and $CH(OCH_2C\underline{H}_3)_2$), MS(chemical ionization) 445(M^++1, 6.3%), 399(100%), 353(97%), 329(32%), 291(19%).

Diethyl 3-(5-methoxy-1-methylsulphonylindolyl)propionamide 208. — A solution of distilled titanium tetrachloride (0.12 cm^3, 1.1 mmol) in dry toluene (3 cm^3) was added dropwise to a solution of diethyl acetal 201 (0.44 g, 1 mmol) in toluene (12 cm^2) at 110 °C under nitrogen. Throughout the addition which lasted 3 min, the reaction mixture was maintained under reflux and was heated for a further 20 min afterwards. When cooled, the resultant

mixture was poured into cold saturated sodium hydrogen carbonate solution (40 cm^3). The aqueous layer was then extracted with ethyl acetate (2x 25 cm^3) and the combined organic layers were washed with water (2x 20 cm^3), saturated brine (20 cm^3), dried ($MgSO_4$), and the solvent removed to yield a solid residue. Column chromatography of the residue on silica gel, eluting with ethyl acetate in petroleum ether, gave the title compound as a colourless solid (31 mg, 9%), m.p.127 °C, UV 223, 257, 263(sh), IR(S) 2940, 1620, 1460, 1370, 1150, ^1H n.m.r. 7.72 (1H,s,7-H), 7.74 (1H,d, J=3.7 Hz,2-H), 7.02 (1H,s,4-H), 6.63 (1H,d,J=3.7 Hz,3-H), 3.88 (3H,s,OCH_3), 3.39 (2H,q,J=7.1 Hz,$NC\underline{H}_2CH_3$), 3.31 (2H,q,J=7.1 Hz,$NC\underline{H}_2CH_3$), 3.08 (2H,m,$C\underline{H}_2CH_2CONEt_2$), 3.07 (3H, s,$SO_2CH_3$), 2.61 (2H,m,$CH_2C\underline{H}_2CONEt_2$), 1.15 (3H,t,J=7.1 Hz, $NCH_2C\underline{H}_3$), 1.12 (3H,t,J=7.1 Hz,$NCH_2C\underline{H}_3$), MS(m/z) 352(M^+, 30%), 321(3%), 279(1%), 273(3%), 251(22%), 141(100%) [Found: C, 57.9; H, 7.0; N, 7.8. $C_{17}H_{24}N_2O_4S$ requires: C, 57.9; H,6.9; N, 7.95%].

Section V

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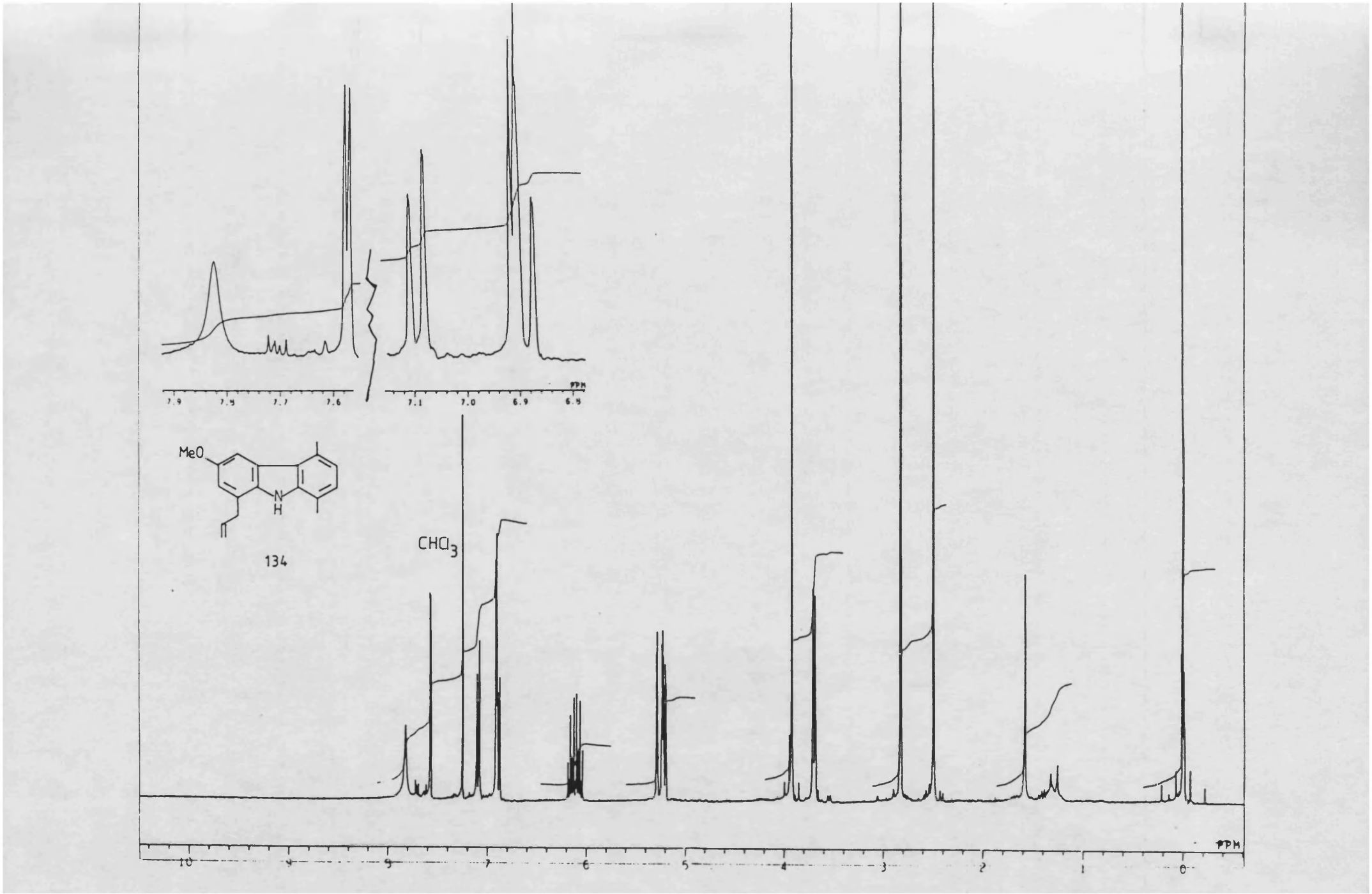
Appendix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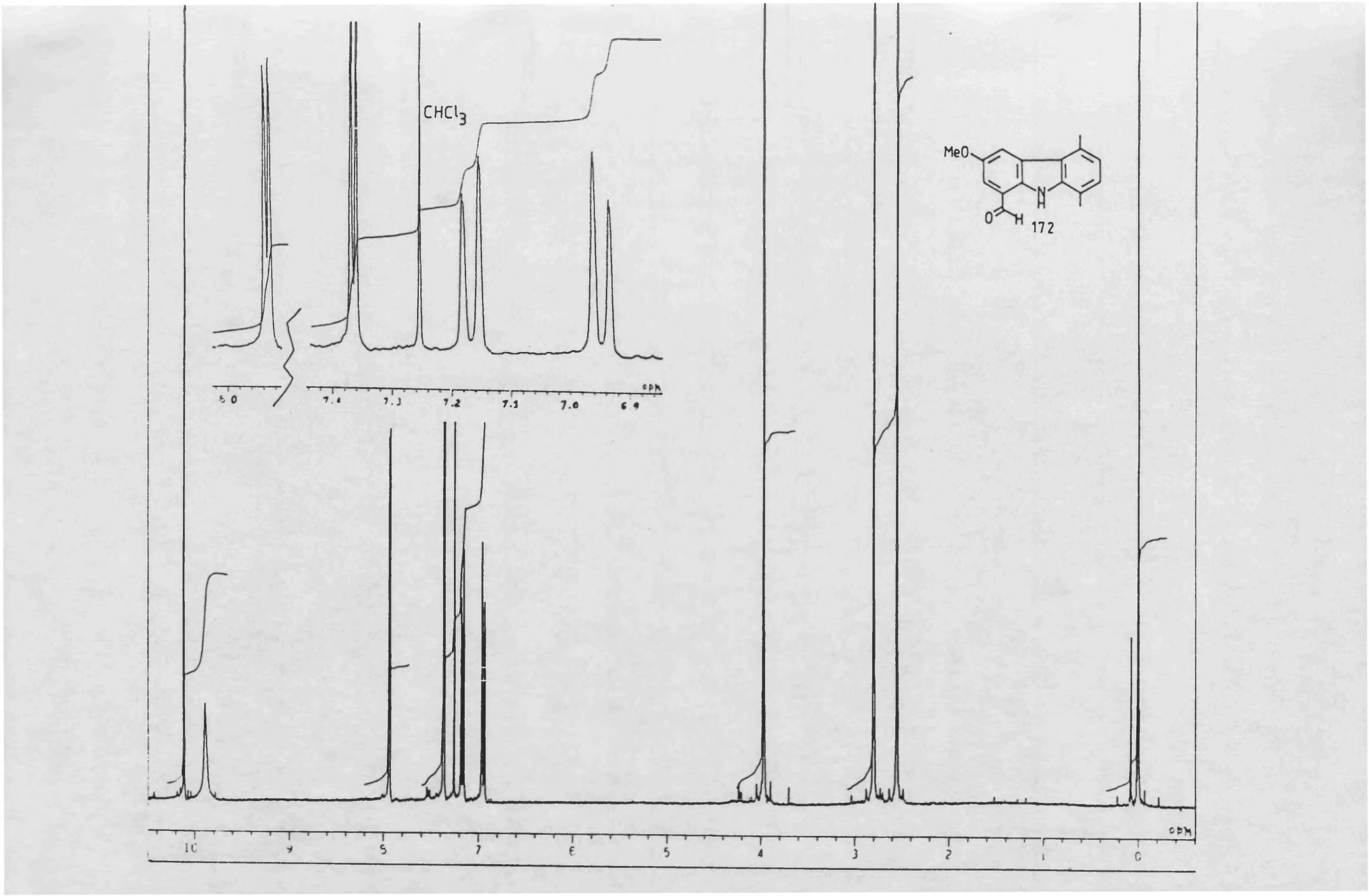
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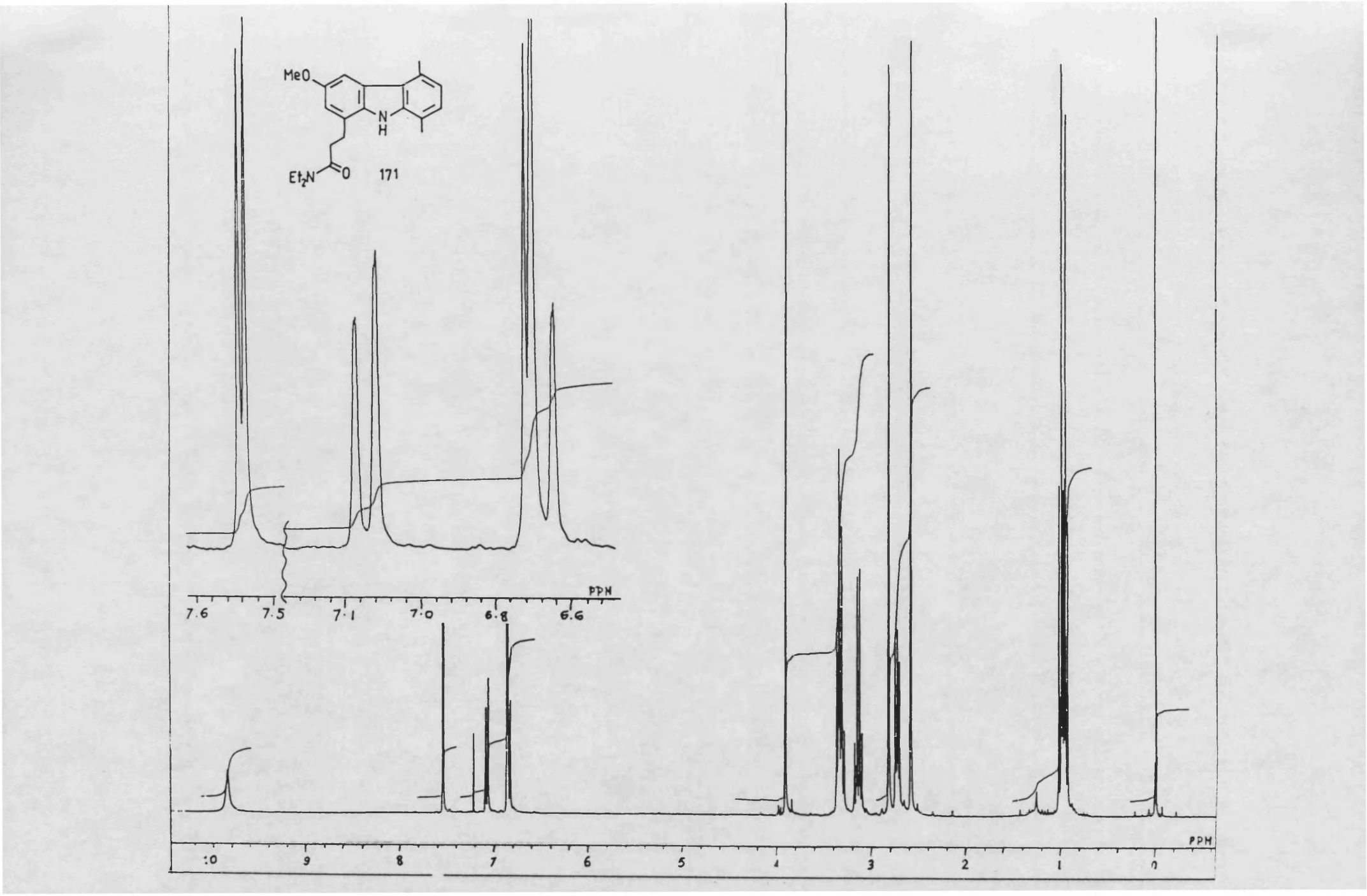
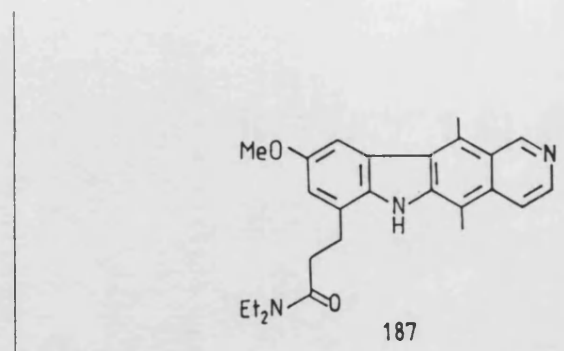
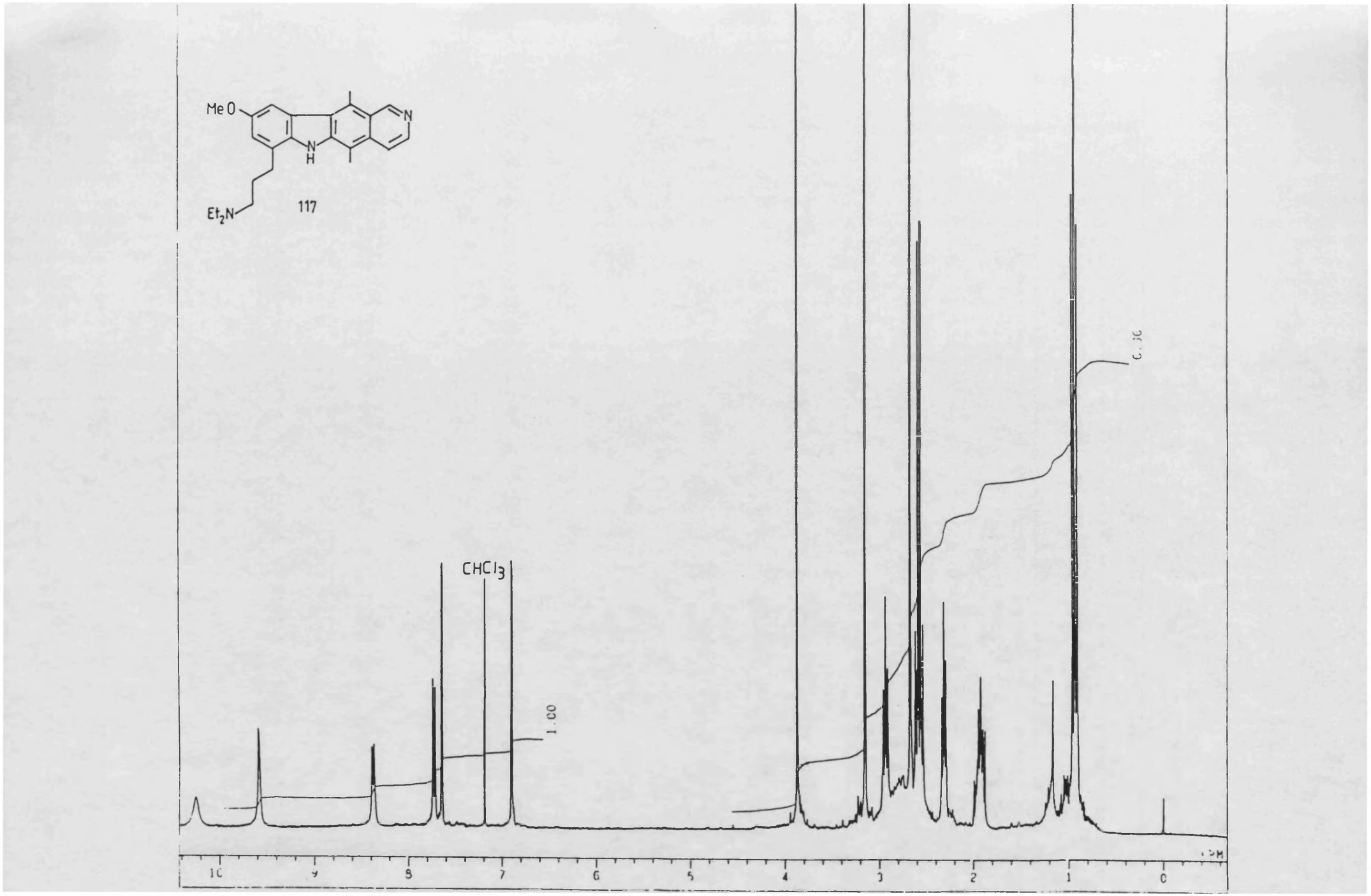
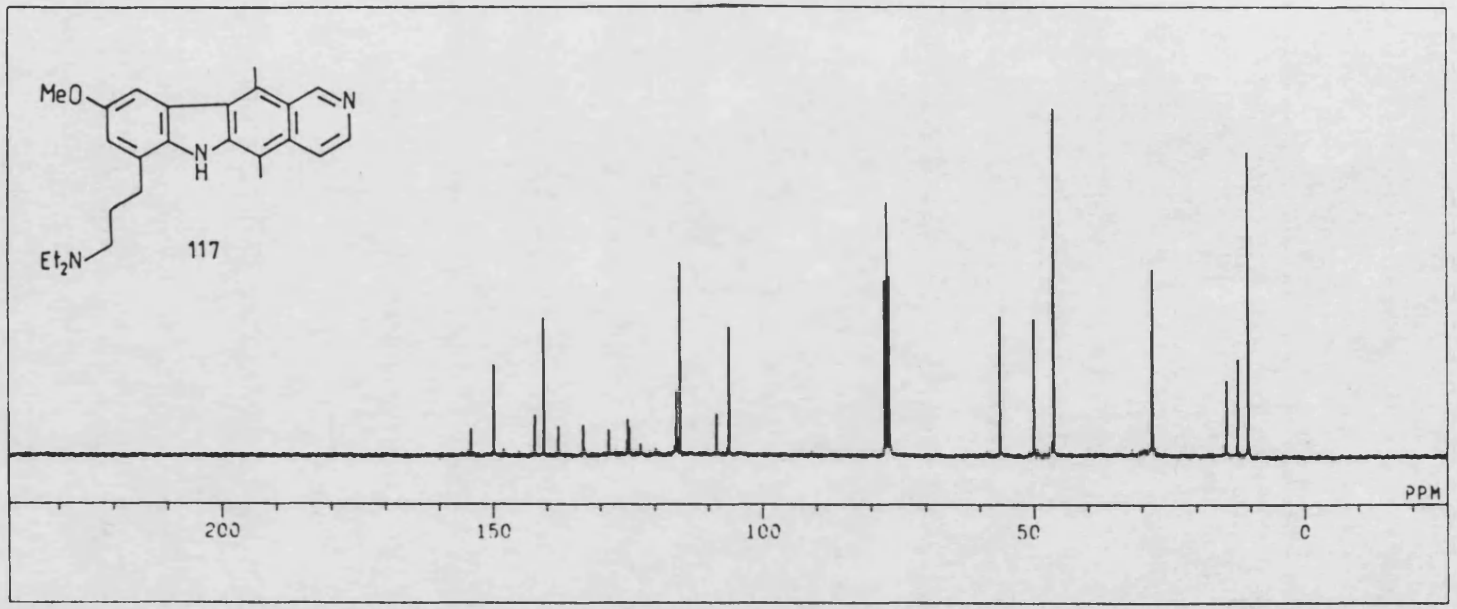

MeO
N
H
Et2N
O
171
PPM
7.6
7.5
7.1
7.0
6.8
6.6
PPM
10
9
8
7
6
5
4
3
2
1
0



187


MeO
N
H
Et2N
117
CHCl3
1.00
6.16
10
9
8
7
6
5
4
3
2
1
0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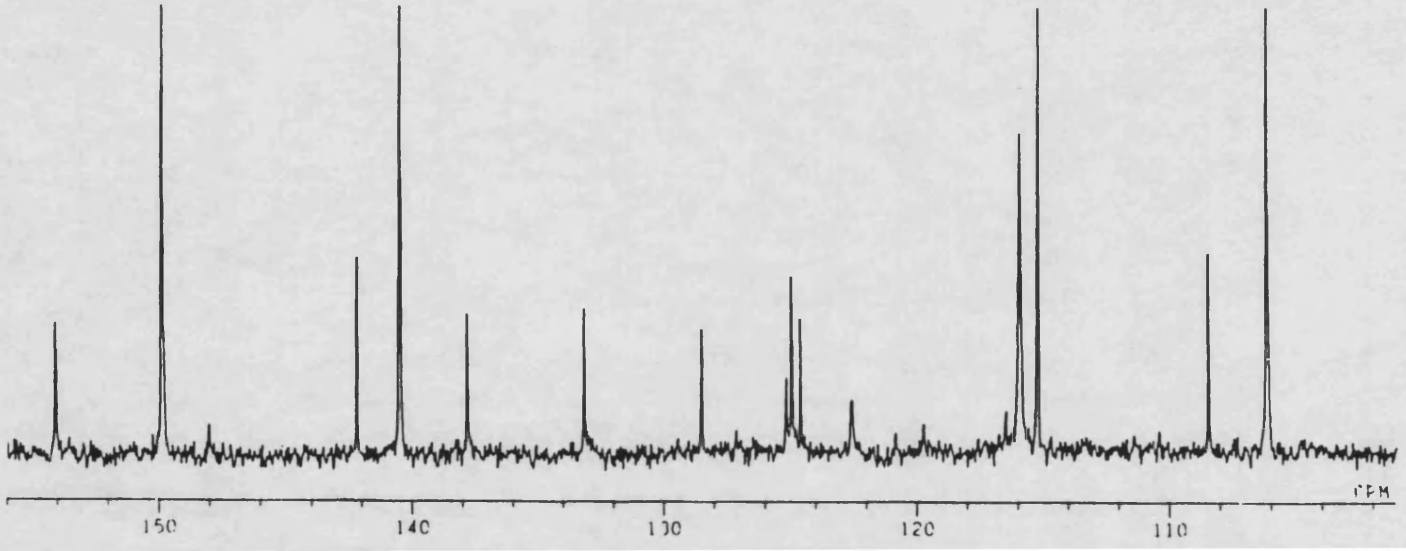
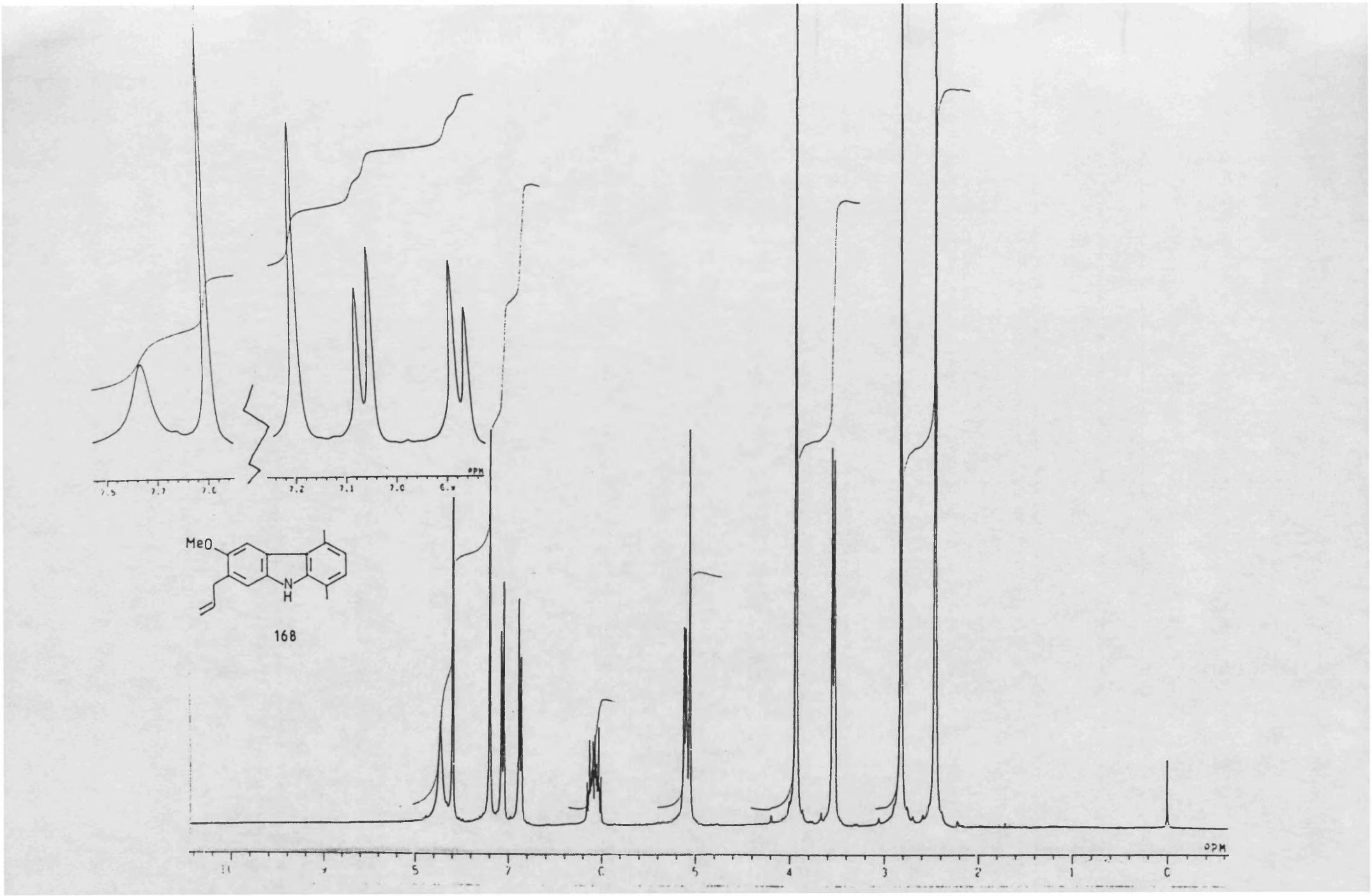
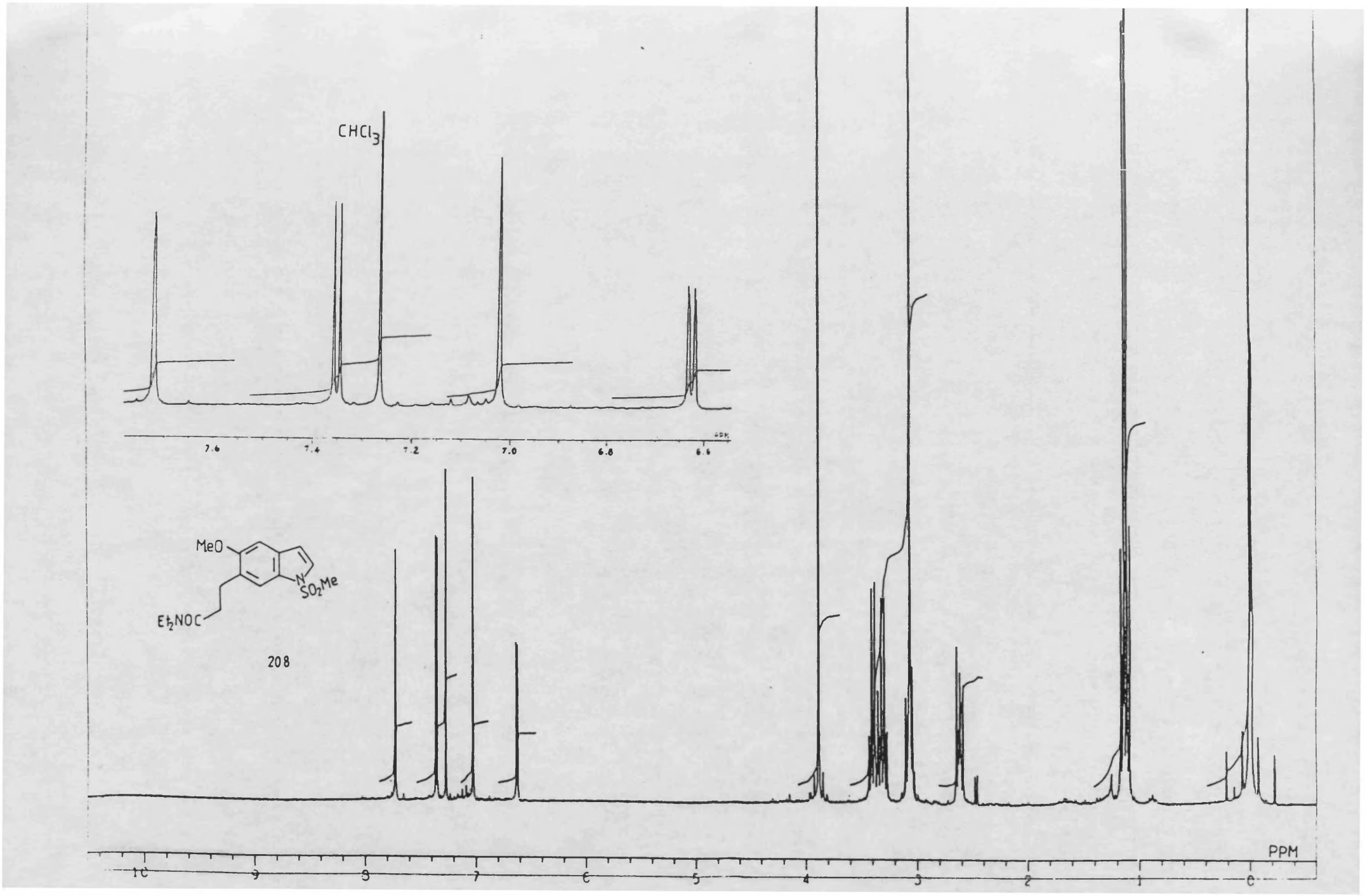
N
H
N
Et2N
117
PPM
200
150
100
50
0


PPM
150
140
130
120
110


MeO
N
H
168
PPM
PPM


CHCl3
7.6
7.4
7.2
7.0
6.8
6.6
MeO
N
SO2Me
Et2NOC
208
PPM
10
9
8
7
6
5
4
3
2
1
0